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Treatment and Long-Term Outcome of COVID-19 Disease in Children with Inborn Errors of Immunity (IEI): Does Hematopoietic Stem Cell Transplantation (HSCT) Have a Protective Effect?

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ABSTRACT

Objective: Data on the risk factors, outcomes, and long-term effects of SARS-CoV-2 infection (COVID-19), especially following hematopoietic stem cell transplantation (HSCT) in pediatric patients with inborn errors of immunity (IEI) are limited. The study aims to define the clinical course of infection and identify risk factors for a worse outcome and long-term effects of COVID-19 in individuals with IEIs and those who have received HSCT for IEIs.

Materials and Methods: In this single-center analysis, we retrospectively analyzed 74 pediatric IEI patients with COVID-19 between March 2020 and March 2023. Sixty-four patients were evaluated about COVID-19's long-term consequences one year after the outbreak.

Results: Most patients exhibited combined immunodeficiency (51%), followed by antibody deficiency (28%), and syndromic combined immunodeficiencies (12%). Two patients had liver transplants, and 27 patients had HSCT before COVID-19. Thirty-two patients (43%) were hospitalized, and 3 (4%) died. The median time from HSCT to COVID-19 infection was 59 months (min 16 days, max 192 months). The major risk factor for infection severity was chronic pulmonary illness. Severe COVID-19 was associated with musculoskeletal abnormalities ($p < 0.001$), chronic lung disease ($p < 0.01$), hypogammaglobulinemia ($p < 0.001$), as well as fever and dyspnea ($p < 0.01$). Higher severity was also linked to the use of immunoglobulin and chemoprophylaxis (both $p < 0.001$). Mortality was significantly higher in patients with autoinflammatory syndromes and innate immune defects ($p < 0.05$). There is no difference between post-HSCT patients and our IEI cohort for COVID-19 illness severity. Remdesivir and convalescent plasma were given to five reinfected-relapsing patients. In total, 28 long-term side effects were identified, with fatigue, hair loss, and red eye being the most common.

Conclusion: Overall, we found that hypogammaglobulinemia, chronic lung disease, and musculoskeletal abnormalities are associated with a severe disease course. The clinical course and outcomes of post-HSCT pediatric patients with COVID-19 are generally favourable. The long-term effects of COVID-19 can be seen in both groups regardless of the clinical severity of the disease.

Keywords: COVID-19, primary immunodeficiency, hematopoietic stem cell transplantation, long-term effects

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INTRODUCTION

In December 2019, Wuhan, China, witnessed the emergence of SARS-CoV-2, a novel positive-sense single-stranded RNA coronavirus that rapidly evolved into a global public health threat (1). SARS-CoV-2 is an infectious disease that can manifest in a variety of presentations, from a moderate cold to life-threatening respiratory failure. Nevertheless, there has been a significant increase in the morbidity and mortality rates overall compared to the broader population (2).

Inborn errors of immunity (IEIs), formerly called primary immunodeficiency disorders, are a growing group of hundreds of disorders (3). IEIs range considerably in severity from mild infections to serious multisystemic disease (4). To support accurate diagnosis and effective clinical management of IEIs, the International Union of Immunological Societies (IUIS) has classified these disorders into ten major categories based on the underlying immunologic defects: 1) combined immunodeficiencies (CIDs); 2) CIDs with associated syndromic features; 3) predominantly antibody deficiencies (PADs); 4) diseases of immune dysregulation; 5) congenital defects of phagocytes; 6) defects in intrinsic and innate immunity; 7) autoinflammatory diseases; 8) complement deficiencies; 9) bone marrow failure syndromes; and 10) phenocopies of IEIs.

In the 2022 IUIS classification, new gene defects associated with susceptibility to COVID-19 infection were defined.[3] The specific immune defects had a key role in highlighting and predicting the course of COVID-19 infection and the treatment strategies. Despite the progress in understanding how COVID-19 may affect patients with IEI, studies focused on the clinical presentation and outcomes of COVID-19 in pediatric patients remain limited (5-11).

Hematopoietic stem cell transplantation (HSCT) represents the definitive curative therapy for several categories of inborn errors of immunity. Both the underlying immunodeficiency and the chemotherapeutic agents used in HSCT conditioning regimens are known to substantially increase susceptibility to infections. However, data describing the clinical manifestations of COVID-19 in immunocompromised patients undergoing bone marrow transplantation remain limited

Symptoms or aberrant clinical parameters enduring for two or more weeks post-COVID-19 start that do not revert to a healthy baseline may be regarded as long-term effects of the disease (12). The impact of age, ethnicity, preexisting health conditions, viral load, or the course of COVID-19 on the risk of developing long-term effects remains unverified (13).

Therefore, we initiated a retrospective study focused on the clinical presentation, laboratory findings, outcomes, and long-term effects of COVID-19 in children and young adult patients with IEI, including those who had undergone HSCT for IEIs. The study aims to define the infection's clinical course and identify risk factors for a worse outcome.

MATERIALS and METHODS

Patients with IEI under follow-up at Ankara University Hospital and who experienced SARS-CoV-2 infection between March 2020 and 2023 were included in this study.

Study Design and Patient Selection

The IEI classification defined by the 2022 International Union of Immunological Societies (IUIS) was used for the classification of the patients (1). SARS-CoV-2 infection was confirmed by reverse transcription–polymerase chain reaction (RT-PCR) performed on nasopharyngeal swab samples. Clinical data for each patient were retrieved retrospectively from medical records.

Definitions

The illness severity of COVID-19 was defined by guidelines of the National Institutes of Health (asymptomatic, mild, moderate, severe, and critical) (14).

- **Asymptomatic or presymptomatic infection:** Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but have no symptoms consistent with COVID-19.
- **Mild illness:** Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.
- **Moderate illness:** Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation value as

measured by pulse oximetry (SpO2) of ≥94% in room air at sea level.

- **Severe illness:** Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.
- **Critical illness:** Individuals who have respiratory failure, septic shock, or multiple organ dysfunction.

Multisystem inflammatory syndrome in children (MIS-C) was defined according to the current 'United States Centers for Disease Control and Prevention' case definition in an individual aged < 21 years (15).

Data Collection

Baseline demographic and clinical characteristics were recorded, including IEI category and molecular diagnosis (when available); comorbidities including respiratory system disorders, cardiovascular disorders, gastrointestinal disorders, endocrine disorders, musculoskeletal disorders, dermatological disorders, presence of chronic infection, and presence of graft versus host disease (GVHD); and medications prior to COVID-19 such as prophylactic antibiotic usage, immunoglobulin replacement therapy, and usage of immunosuppressive drugs. As for the baseline immunological assessment, information collected included immunoglobulin levels, number and percentage of white blood cells (WBC), neutrophils, lymphocytes, T lymphocytes (CD3 +), helper T cells (CD4 +), cytotoxic T cells (CD8 +), B cells (CD19 +), and NK cells (CD16+CD56+). In the group of patients requiring hospitalization, when available, we collected data about the number of white blood cells (WBC), neutrophils, lymphocytes, lactate dehydrogenase (LDH), albumin, ferritin, IL-6, D-dimer, procalcitonin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, troponin, pro-BNP, chimerism (for HSCT recipients), echocardiographic assessment, need of pediatric intensive care (PICU) admission, oxygen requirement, need of non-invasive ventilation, need of mechanical ventilation, and duration of hospitalization.

One year after the pandemic, all patients were questioned for clinical symptoms that did not exist before COVID-19 infection but appeared later and persisted for more than two months.

Eight patients could not be included in the long-term effects questionnaire due to death.

Statistical Analysis

SPSS v.26 and Excel were used for statistical analysis and to produce all the graphs. We calculated the median and interquartile range for continuous variables and the frequency and percentage for the categorical variables. Normality was evaluated with the Kolmogorov-Smirnov test. The non-parametric data were analyzed with the Mann-Whitney U and Kruskal-Wallis H tests. The chi-square test or Fisher's exact test (when the chi-square test assumptions did not hold due to low expected cell counts) was used to analyze relationships between categorical variables via cross-tabulation.

We performed correlations between variables: sex, median age, group of IEI, type of comorbidities, medication use before COVID-19 infection, type of clinical manifestation, laboratory findings, and severity of COVID-19 infection.

We used the Kendall tau-b and the Kendall tau-c correlation coefficient for correlation between ordinal variables. The logistic regression model was used to examine the association of variables when the dependent variable's outcome was binary.

RESULTS

Clinical Features

We obtained data from 74 patients with IEIs, all of whom had SARS-CoV-2 infection confirmed by RT-PCR performed on nasopharyngeal swab samples. IEI had been diagnosed before the onset of COVID-19 in all patients except one, who was identified to have LPIN2 deficiency during hospitalization for COVID-19.

The median age at the time of the study was 8.5 years (min. 4 months, max. 28 years). Only five patients were over 18 years old and had been followed up at our institution since their childhood. The male-to-female ratio was 1.24:1.

The highest proportion of COVID-19 in IEI patients was found in CID (n=29/39%), followed by PAD (n=21/28%), syndromic CID (n=9/12%), phagocyte system defects (n=8/11%), immune dysregulations (n=3/4%), autoinflammatory diseases (n=2/3%), and innate immu-

nity defects (n=2/3). Due to vaccine shortages at the start of the COVID-19 pandemic, none of the IEI patients were fully vaccinated. One patient contracted SARS-COV-2 despite two vaccinations and developed flu-like symptoms. Nine patients were vaccinated at least one time after COVID-19.

Asymptomatic infection occurred in 6 (8%) patients. Three asymptomatic patients were tested for SARS-CoV-2 RT-PCR because they were hospitalized for reasons other than COVID-19, while the other three were examined because of past contact with a positive case.

Mild disease was the most common presentation (n=45, 61%), followed by moderate disease in 13 patients (17.6%), severe disease in 5 (6.8%), and critical disease in 5 patients (6.8%). The distribution of COVID-19 severity in IEI types is shown in Figure 1A. There was no correlation between sex and the severity of infection (Kendall's tau-c 0.210, p=0.621 Fisher exact test). No significant difference was identified between mild, moderate, severe, and critical cases for age (One-way ANOVA p=0.140).

Before COVID-19, 27 (36.5%) patients had received HSCT, two also had liver transplants. Thirty-two (43%) patients were receiving intravenous immunoglobulin (IVIG) replacement therapy, and 12 (16%) were receiving subcutaneous immunoglobulin (SCIG). Chemoprophylaxis had been used in 51 (69%) patients; 48 received trimethoprim-sulfamethoxazole, 22 received acyclovir/ganciclovir, and three received azithromycin. Granulocyte colony-stimulating factor (GCSF) had been used in 9 cases. There was a strong correlation between the use of immunoglobulin (Kendall tau-c 0.319, $p < 0.001$) and the use of

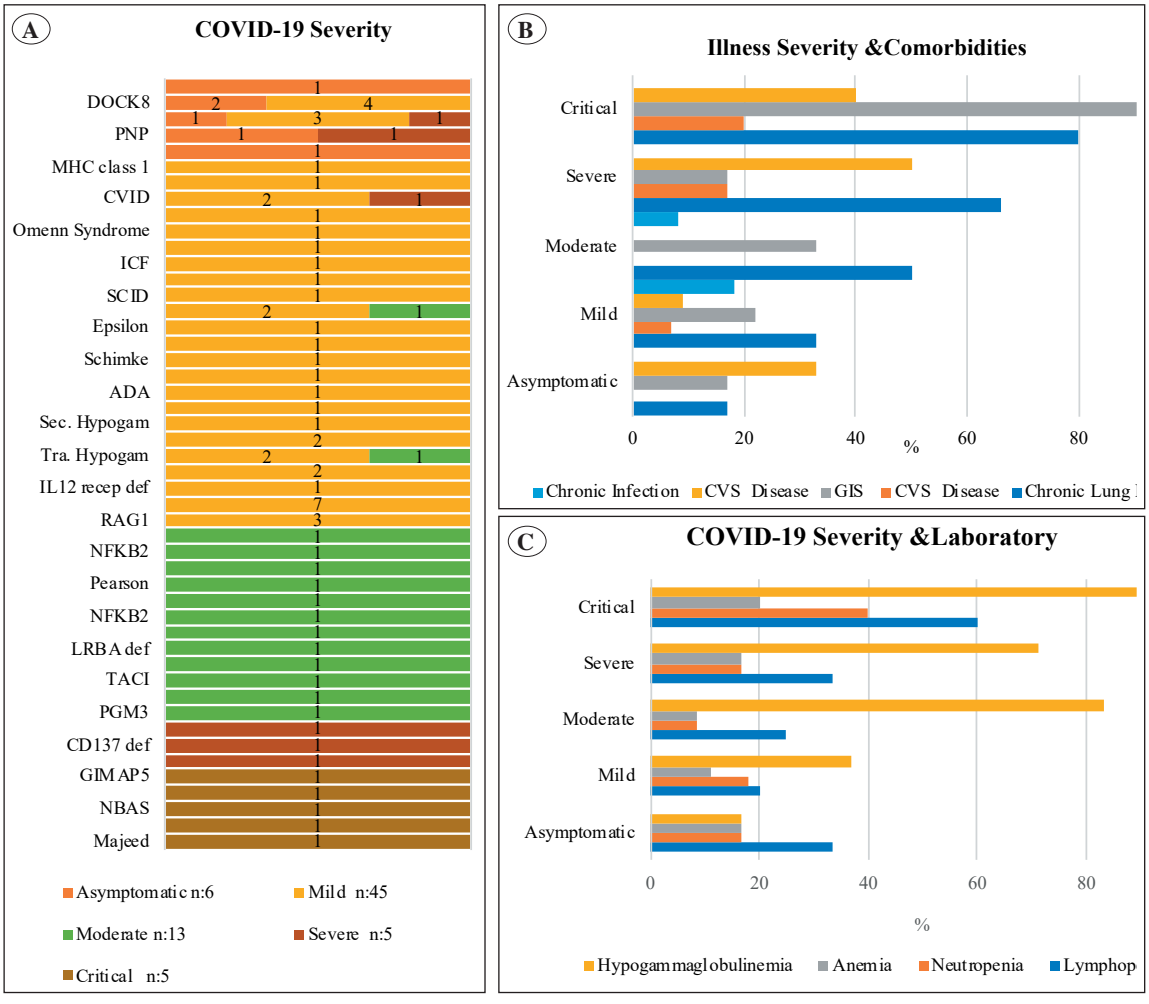


Figure 1: COVID-19 severity. **A)** COVID-19 severity according to types of IEI diagnosis. **B)** Association between severity of COVID-19 and comorbidities. **C)** Association between COVID-19 illness severity and laboratory findings

chemoprophylaxis (Kendall tau-c 0.305, $p < 0.001$) with higher severity of COVID-19.

Before COVID-19, 20 patients (27%) used immunosuppressive agents, including steroids (n:2), mycophenolate mofetil (n:3), tacrolimus (n:3), budesonide (n:3), cyclosporine (n:2), ustekinumab (n:2), sirolimus (n:1), abatacept (n:1), and colchicine (n:1). Inhaled steroids were used by 18 (24.3%) patients. The severity of COVID-19 did not correlate with the usage of immunosuppressive medications or inhaled steroids.

For 71/74 patients, the symptoms of COVID-19 were documented. Fever was the most prevalent symptom in 50/71 (67%), followed by cough in 24 (32%), dyspnea in 14 (19%), sore throat in 9 (12%), and runny nose in 7 (9.5%). Myalgia/fatigue was present in 15 (18%) patients, and headache in 6 (8.4%) patients. Gastrointestinal symptoms were reported in four patients, including nausea in one and diarrhea in three. The severity of infection was strongly correlated with fever and dyspnea (Kendall tau-c 0.324, $p < 0.01$).

Comorbidities were absent in 21(28%) patients while at least one comorbidity was observed in 53 (72%). Chronic lung diseases represented the predominant comorbidity with 30 (44%) patients, including bronchiectasis in 22 and moderate asthma in 4 patients. Additional baseline structural lung alterations included pulmonary nodules and atelectasis. Gastrointestinal disorders were detected in 22 patients (30%), dermatological conditions in 15 (20%), skeletal system abnormalities in 9 (12%), chronic infection in 6 (8%), and cardiovascular comorbidities in 6 (8.1%), respectively. In terms of comparing comorbidities, musculoskeletal system abnormalities (Kendall tau-c 0.497, $p < 0.001$), and chronic lung disorders (Kendall tau-c 0.193, $p < 0.01$) were correlated with the severity of illness. The relationship between comorbidities and the clinical severity of COVID-19 is demonstrated in Figure 1B.

Baseline immunological tests showed lymphopenia in 20/74 (27%) patients, while 14/74 (20%) showed neutropenia. Lymphopenia involved the CD3 + compartment in 21/71 (28%) patients, the CD4 + in 27/71 (36.5%), the CD8 + in 19/71, the CD19 + in 20/71 (27%), and the CD3-CD16-CD56+ in 34/71 (48%). Twenty-seven of the 36 patients with hypogammaglobulinemia had pan-hypogammaglobulinemia. The severity of COVID-19 was substantially linked with hypogammaglobulinemia (Kendall tau-b 0.398, $p < 0.001$), but not with other laboratory values. Lab results and COVID-19 severity are shown in Figure 1C. Fourteen patients underwent echocardiographic (ECHO) evaluation. ECHO findings were normal in nine patients and abnormal in five with pericardial effusion (2), hypertrophic cardiomyopathy (1), left ventricular systolic dysfunction (1), and mild septal hypertrophy (1), respectively.

Out of 74 patients, 42 were treated on an outpatient basis, while 32 (43%) required hospitalization. Eight patients were admitted to the hospital for reasons unrelated to COVID-19 (2 asymptomatic, 6 mild symptoms). Despite having moderate COVID-19 symptoms, two were hospitalized for unrelated reasons (CMV viremia, ZAP-70 deficiency for HSCT).

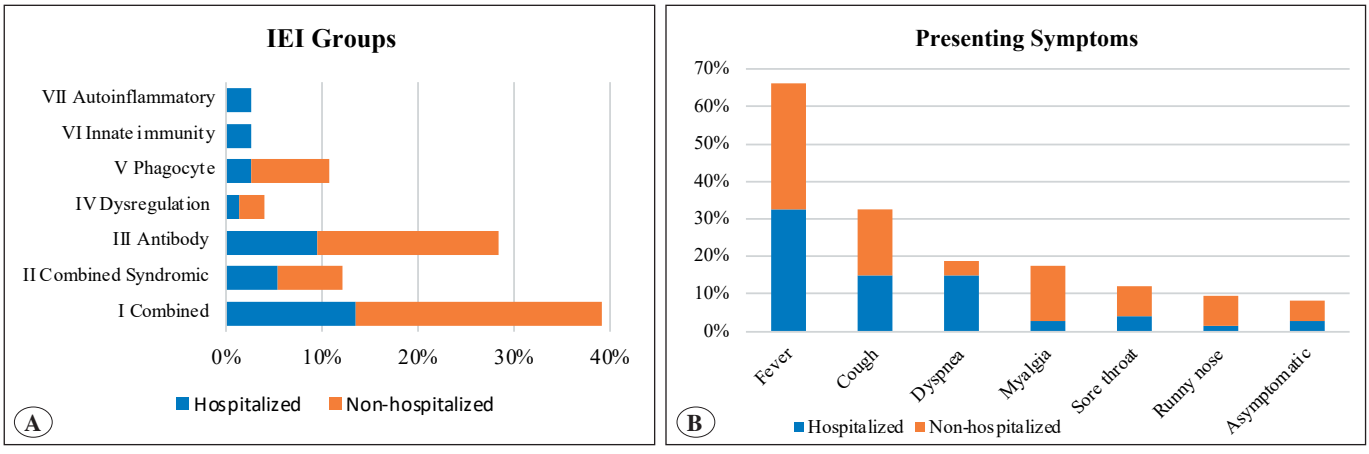


Figure 2: Clinical features of COVID-19/IEI patients. **A)** IEI groups in the hospitalized patients and the non-hospitalized patients **B)** Main presenting symptoms of COVID-19 in the hospitalized patients and the non-hospitalized

Hospitalization rates were highest in CID, with 13 patients (54%). All patients with autoinflammatory diseases (n=2) and innate immunity defects (n=2) (one with another indication) were hospitalized. The remaining IEI groups of hospitalized patients are indicated in Figure 2A. There was no significant difference in hospitalization status across IEI groups (p. 0.324).

Fever was the predominant symptom leading to hospitalization (91%) and was significantly more common in hospitalized than in non-hospitalized patients ($p < 0.05$). Dyspnea was the second most prevalent symptom (47.8%) and was markedly more common among hospitalized patients ($p < 0.0001$). Fever and dyspnea increased the risk of hospitalization by 1.92-fold and 2.44-fold, respectively ($p=0.015$ and $p=0.002$). The primary symptoms associated with hospitalization are illustrated in Figure 2B.

Treatment and Outcome

Treatment for COVID-19 infection differed according to the observation period. Five patients received treatment at various facilities and were excluded from the analysis due to a lack of detailed medication information. One patient was admitted to the PICU for respiratory distress induced by COVID-19, while being monitored for GIMAP-5 deficiency and undergoing chemotherapy for lymphoma, and subsequently succumbed to respiratory failure.

Sixty-seven patients (90%) recovered without complications. Six patients experienced COVID-19 reinfection, one had a prolonged infection, and three exhibited both reinfection and prolonged infection. Although these patients had different underlying IEI diagnoses, they shared a common immunologic feature: B-cell lymphopenia and/or a B-cell functional defect. Prolonged infection and reinfection were significantly more frequent in hospitalized compared with non-hospitalized patients ($p < 0.05$). All patients with prolonged infection and/or reinfection were receiving IVIG replacement therapy.

Detailed information for respiratory support was available for 22/24 patients. Six required supplemental oxygen via mask for hypoxia. Nine patients were admitted to the intensive care unit (ICU): eight for respiratory distress and one for cardiac failure. Five patients required noninvasive ventilation (NIV), three required invasive ventilation, and one of them required high-frequency oscillation. Seven of nine requiring ICU had a history of chronic lung disease. Additional comorbidities included one patient with hypotonia, one with ventricular septal defect, one with surgically treated aortic coarctation, one with dilated cardiomyopathy, one with type I diabetes mellitus, one with hypothyroidism, and one with Hodgkin lymphoma.

The majority of infected patients survived and fully recovered from acute disease. Three patients, early in the pandemic, died from COVID-19, and the mortality rate was 4%.-A total of five patients had MIS-C. When the IEI groups were compared in terms of mortality, the autoinflammatory syndrome and innate immune system defect had significantly higher mortality than the other groups ($p < 0.05$).

Post-HSCT Patients

Twenty-seven patients had previously undergone HSCT. The median time after HSCT was 59 months and ranged between 16 days to 192 months. Eighteen of them had full chimerism, and nine had mixed chimerism. B-cell engraftment was not achieved in eleven patients. The median age was 9 years (min 1 year, max 21 years). The male-to-female ratio was 1.45:1. CID represented the most common IEI in 20 (74%), followed by syndromic CID in 3 (11%), phagocyte system defect in 3 (11%), and immune dysregulation in one (4%). Illness severity was asymptomatic in 3, mild in 19, moderate in 3, and severe in 2 patients. The characteristics and outcomes of bone marrow transplant patients are shown in Table I.

Long-Term Effects of COVID-19

Twenty-four of the 66 patients who completed the long-term side-effect questionnaire reported at least one long-term side effect. The most common long-term symptom was fatigue (n=12), and the others were hair loss (n=8), red eye (n=7), sleep disorders (n=6), cutaneous manifestations (n=6), and post-activity polypnea (n=6). There was no correlation between COVID-19 illness severity and long-term side effects of COVID-19 infection. No significant difference was observed in the long-term effects of COVID-19 after transplantation. The long-term side effects of COVID-19 infection in IEI patients are shown in Table I and Table II.

Table I: Characteristics, outcomes and long-term effects of 27 patients with IEI and COVID-19 infection post-hematopoetic stem cell transplantation

Patient	Sex	Age (years)	IUIS IEI classification category	Specific diagnosis	Comorbidities	Time post-HSCT (months)	Clinical Manifes-tations	Chimerism			Severity of CO-VID-19 infection	Required hospital admission	Required ICU admission	Treatment		Outcome	Long-term Effect
								T (%)	Myeloid (%)	B (%)				Medications used	Respiratory Support		
P48	Female	1	I Combined	RAG1 deficiency	None	2,5	Fever	96	27	0	Mild	No	No	None	None	Recovered	None
P49	Male	1	I Combined	IL-7 deficiency	GIS GVHD	4	Fever, runny nose	89	6	9	Mild	No	No	None	None	Recovered	None
P50	Female	1,5	I Combined	ZAP-70 deficiency	GIS GVHD	15 days	Fever, diarrhea, dyspnea	92	97	-	Moderate	Yes	No	Antibiotic therapy	Mask O2	Recovered	Cutaneous manifesta-tions, sleep disorder, chills, red eyes
P51	Male	2	I Combined	CID	BCGitis	20	Fever	99	96	99	Mild	No	No	None	None	Recovered	None
P52	Male	4	I Combined	RAG1 deficiency	Polio sequelae, atelectasis, pul-monary nodule, hydronephrosis	36	Fever	97	6	42	Mild	Yes	No	favipiravir, IVIG	None	Recovered	None
P53	Female	5	I Combined	ADA deficiency	Mental retarda-tion	60	Runny nose	96	5	76	Mild	No	No	None	None	Recovered	None
P54	Female	5	I Combined	DOCK8 deficiency	None	42	Runny nose	45	2	9	Mild	No	No	None	None	Recovered	Sore throat
P55	Female	6	I Combined	MHC class II deficiency	None	60	Myalgia	79	6	na	Mild	No	No	None	None	Recovered	None
P56	Male	6	I Combined	Epsilon Defect	Skin GVHD	72	Fever, cough	91	3	na	Mild	No	No	Favipiravir	None	Recovered	Fatigue
P57	Male	9	I Combined	T-B-NK+ SCID	Bronchiolitis obliterans	89	Fever, runny nose	98	4	na	Mild	No	No	None	None	Recovered	None
P58	Male	10	I Combined	RASGRP1 deficiency	Bronchiectasis	15	Cough, diarrhea	99	99	99	Mild	No	No	None	None	Recovered	None
P59	Male	10	I Combined	RAG1 deficiency	Cerebral palsy	0	Fever, headache, cough	96	5	13	Mild	No	No	None	None	Recovered	None
P60	Male	10	I Combined	DOCK8 deficiency	GIS GVHD	7	Runny nose, cough	54	96	na	Mild	No	No	None	None	Recovered	None
P61	Female	11	I Combined	ITK deficiency	Bronchiectasis	70	Fever	99	98	na	Mild	No	No	None	None	Recovered	None
P62	Female	11	I Combined	Omenn syndrome	Bronchiolitis obliterans, dermatitis	144	Fever	100	na	na	Mild	Yes, other indication	No	Antibiotic therapy	None	Recovered	Fatigue, hair loss, chest pain
P63	Male	12	I Combined	IL-7 deficiency	None	132	Fever, joint pain	94	na	na	Mild	No	No	None	None	Recovered	Fatigue, headache, ageusia

Table I continue

P64	Female	16	I Combined	NIK deficiency	Bronchiectasis, atelectasis, pulmonary nodules, rheumatoid arthritis, osteopenia, growth retardation	96	Fever, dyspnea, myalgia	100	100	0	Severe	Yes	No	Favipiravir, Antibiotic therapy	NIV	Recovered from COVID-19 infection, died from non COVID-19 cause	-
P65	Male	17	I Combined	Artemis defect	Skin GVHD, GI GVHD, bronchiectasis, pulmonary GVHD	22	Fever, nausea	96	99	95	Moderate	Yes	No		Mask O2	Recovered	Cutaneous manifestations
P66	Male	21	I Combined	DOCK8 deficiency	Chronic hepatitis B infection	57	Fever, sore throat	98	92	98	Mild	No	No	Favipiravir	None	Recovered	Post-activity polypnea
P67	Male	2,5	II Combined Syndromic	PNP deficiency	Growth retardation, bladder dysfunction (hemorrhagic cystitis)	18	Asymptomatic	75	11	-	Asymptomatic	No	No	Favipiravir	None	Recovered	None
P68	Male	4	II Combined Syndromic	PGM3 deficiency	Epilepsy and p.carinatum, pulmonary nodule, hydroureteronephrosis	42	Fever, cough, dyspnea	97	96	97	Severe	Yes	NA	Favipiravir	NA	Recovered	Post-activity polypnea
P69	Male	18	II Combined Syndromic	PNP deficiency	Cerebral palsy	192	Fever, cough	93	8	0	Severe	Yes	Yes	Favipiravir, ASA, steroids, IVIG, antibiotic therapy, convalescent plasma	NIV	Two COVID-19 infection, recovered	None
P70	Male	3	IV Dysregulation	Chediak-Higashi Syndrome	None	30	Fever	98	99	99	Mild	No	No	Antibiotic therapy	None	Recovered	None
P71	Female	5	V Phagocyte	LAD1	None	41	Fever, cough, sore throat	98	98	na	Mild	No	No	None	None	Recovered	None
P72	Female	15	V Phagocyte	LAD1	Bronchiectasis	108	Fever	100	100	100	Mild	No	No	None	None	Recovered	Joint pain, chest pain, anxiety, sleep disorder, red eyes
P73	Female	14	I Combined	DOCK8 deficiency	Skin GVHD GI GVHD, liver transplanted	72	Asymptomatic	99	100	na	Asymptomatic	No	No	None	None	Recovered	None
P74	Male	16	V Phagocyte	LAD1	None	144	Asymptomatic	100	100	98	Asymptomatic	No	No	Favipiravir	None	Recovered	None

ADA: Adenosine deaminase, **ASA:** Acetylsalicylic acid, **CID:** Combined immunodeficiency, **GI:** Gastrointestinal, **GVHD:** Graft-versus-host disease, **MV:** Mechanical ventilation, **NIV:** Non-invasive ventilation, **PNP:** Purine nucleotide phosphorylase.

Table II: Characteristics, treatment, outcomes and long-term side effects of 47 patients with IEI and COVID-19 infection

Patient	Sex	Age (years)	IUIS IEI classification category	Specific diagnosis	Comorbidities	Clinical Manifestations	Severity of COVID-19 infection	Required hospital admission	Required ICU admission	Treatment		Outcome	Long-term Effect
										Medications used	Respiratory Support		
P1	Male	7	CID	IL2RG defect	-	Fever	Moderate	Yes	No	Favipiravir, IVIG	None	Recovered	None
P2	Male	7	CID	DOCK8 deficiency	Bronchiectasis, scoliosis	Sore throat	Mild	No	No	None	None	Recovered	Fatigue, sputum
P3	Male	8	CID	CID	Lymphoma	Fever	Mild	No	No	None	None	Recovered	None
P4	Male	17	CID	ICOS deficiency	IBD, hypothyroidism, chronic lung disease	Fever, sore throat, dyspnea	Critical	Yes	Yes	Favipiravir, IVIG, remdesivir, enoxoparin, convalescent plasma	NIV	Persistent, two COVID-19 infection, Recovered	Fatigue, hair loss, post-activity polypnea, cough, sweat, nausea, tinnitus, anxiety, weight loss, sleep disorder, chills, red eyes
P5	Male	17	CID	LRBA deficiency	Peripheral neuropathy	Fever, cough, headache, myalgia, chest pain	Moderate	Yes	No	Steroids	None	Recovered	Hair loss, general pain, nausea, sleep disorder, red eyes, sore throat
P6	Male	17	CID	DOCK8 deficiency	Autoimmune haemolytic anemia, eczema, chronic lung disease	Asymptomatic	Asymptomatic	Yes, other indication	No	Antibiotic therapy	Mask O2	Recovered	None
P7	Female	20	CID	GIMAP5 defect	Lymphoma	NA	Critical	Yes	Yes	NA	MV	Recovered from COVID-19 infection, died caused by lymphoma	-
P8	Female	22	CID	CID	Psoriasis vulgaris, Crohn disease	NA	Mild	No	No	None	None	Recovered	Fatigue, ageusia
P9	Female	25	CID	MHC class 2deficiency	Addison's Disease, chronic HBV carrier, hypothyroidism	Sore throat	Mild	No	No	None	None	Recovered	Fatigue, hair loss, joint pain, cutaneous manifestations
P10	Male	0	Syndromic CID	WAS	Thrombocytopenia, eczema	Asymptomatic	Asymptomatic	Yes, other indication	No	None	None	Recovered	None
P11	Male	2	Syndromic CID	Incomplete DiGeorge Syndrome	Corrected coarctation of aorta, VSD, short stature, atelectasis, diaphragmatic hernia	Fever, dyspnea	Severe	Yes	Yes	Steroids, furosemide, inhaled steroids, NIV	NIV	Two COVID-19 infection, Recovered	None
P12	Female	5	Syndromic CID	DIAPH-1 deficiency	Epilepsy, pulmonary nodule	Fever, diarrhea	Mild	Yes, other indication	No	Favipravir, IVIG	None	Persistent, twice COVID-19 infection, recovered, died caused by hepatic failure	-
P13	Female	6	Syndromic CID	Schimke immunoosseous dysplasia	Nephrotic syndrome, iris coloboma, growth retardation, PDA	Fever	Mild	No	No	None	None	Recovered	None
P14	Female	18	Syndromic CID	NFKB1 deficiency	Asthma	Sore throat, fever, chest pain, cough, dyspnea	Moderate	No	No	Favipravir	None	Recovered	Hair loss, post-activity polypnea
P15	Male	10	Syndromic CID	ICF syndrome	-	Fever	Mild	No	No	None	None	Recovered	None
P16	Female	1	PAD	Unclassified hypogammaglobulinemia	-	Fever, cough, runny nose	Mild	No	No	None	None	Recovered	None
P17	Male	1,5	PAD	Transient hypogammaglobulinaemia	Corrected VSD, bilateral hydronephrosis	Fever, cough	Mild	No	No	None	None	Recovered	Fatigue, sleep disorder, red eyes, cutaneous manifestations

Table II continue

P18	Male	1,5	PAD	Transient hypogammaglobulinaemia	Atopic dermatitis	Feveri cough	Mild	No	No	None	None	Recovered	None
P19	Male	1,5	PAD	Transient hypogammaglobulinaemia	Esophageal atresia, aspiration pneumonia, swallowing dysfunction, thyroid agenesis, ASD	Cough	Mild	No	No	Steroids	Mask O2	Recovered	None
P20	Female	3,5	PAD	FNIP1 deficiency	Dilated cardiomyopathy, bronchiectasis	Dyspnea	Critical	Yes	Yes	Remdesivir (2 cures), IVIG, Convelasant plasma	NIV	Two COVID-19 infection, died	-
P21	Male	5	PAD	Unclassified hypogammaglobulinemia	Food allergy	Fever, cough, dyspnea	Mild	No	No	None	None	Recovered	None
P22	Male	6	PAD	Unclassified hypogammaglobulinemia	Allergic asthma	Dyspnea	Mild	No	No	None	None	Recovered	None
P23	Female	8	PAD	Bruton's agammaglobulinemia	Giardiasis	Fever	Mild	Yes, other indication	No	None	None	Recovered	None
P24	Male	9	PAD	Unclassified hypogammaglobulinemia	Asthma	Fever, headache, joint pain	Mild	No	No	None	None	Recovered	None
P25	Female	9	PAD	Unclassified hypogammaglobulinemia	Asthma	Headache, myalgia	Mild	No	No	None	None	Recovered	None
P26	Female	9	PAD	Unclassified hypogammaglobulinemia	-	Fever	Mild	No	No	None	None	Recovered	None
P27	Male	11	PAD	Bruton's agammaglobulinemia	-	Fever, cough	Moderate	Yes	No	Favipravir, steroids, Remdesevir, Convalescent plasma	Mask O2	Twice COVID-19 infection, Recovered	Anxiety
P28	Female	13	PAD	Unclassified hypogammaglobulinemia	Lymphoma	Fever, cough, joint pain	Mild	No	No	None	None	Recovered	Fatigue, hair loss, post-activity polypnea, joint pain, depression, cutaneous manifestations, sleep disorders
P29	Male	14	PAD	CVID	Giardiasis	Cough	Mild	No	No	None	None	Recovered	None
P30	Male	15	PAD	Bruton's agammaglobulinemia	-	Fatigue	Mild	No	No	None	None	Recovered	None
P31	Female	16	PAD	Selective Ig A deficiency	Nephrotic syndrome	NA	Mild	No	No	Favipravir	None	Recovered	None
P32	Male	17	PAD	TACI deficiency	Asthma, hepatosteatosis, pulmonary nodule	Fever, runny nose, cough	Moderate	Yes	No	Ivıg, favipravir	None	Two COVID-19 infection, recovered	Fatigue
P33	Female	17	PAD	Ig M heavy chain mu defect (agammaglobulinemia)	-	Dyspnea, headache, joint pain, sore throat	Moderate	No	No	None	None	Recovered,	None
P34	Male	28	PAD	NFKB2 deficiency	Hearing loss, bronchiectasis, pulmonary nodules, candida esophagitis	Fever, cough, dyspnea	Moderate	Yes	No	Favipravir, IVIG, enoxoparine	Mask O2	Twice COVID-19 infection, recovered, died from non-COVID-19 cause	-

Table II continue

P35	Female	28	PAD	CVID	Bronchiectasis, pulmonary nodule, interstitial lung disease	Fever, dyspnea	Moderate	Yes	Yes	Remdesevir, convelasant plasma	MV	Recovered	Fatigue
P36	Female	2,5	PAD	Secondary hypogammaglobulinemia	Biliary atresia, liver transplantation, atelectasis, mosaic attenuation	Fever	Mild	Yes, other indication	No	Gancyclovir	None	Recovered	Hair loss, sweat, cutaneous manifestations
P37	Male	9	Immune dysregulation	CD137 deficiency	Asthma, lymphoma	Fever, cough	Severe	Yes	No	Favipravir, IVIG, steroids	Na	Recovered from COVID-19 infection, death caused by lymphoma	-
P38	Male	12	Immune dysregulation	APECED	Alopecia, Mucocutaneous candidiasis	Fever	Mild	No	No	None	None	Recovered	Weight loss, general pain
P39	Male	1	Phagocyte defect	HAX1 deficiency	Bcgitis	Fever, cough	Mild	Yes, other indication	No	Antibiotic therapy	Mask O2	Recovered	None
P40	Female	1,5	Phagocyte defect	Pearson's Syndrome	Exocrine pancreatic insufficiency	Fever	Moderate	No	No	None	None	Recovered	None
P41	Male	3	Phagocyte defect	LAD1		Fever	Mild	No	No	None	None	Recovered	None
P42	Female	4	Phagocyte defect	LAD1	Tip I Diabetes mellitus	Fever, cough, dyspnea, palpitation	Severe	Yes	Yes	Digoxin, IVIG, furosemide	Mask O2	Recovered	Fatigue, headache, anosmia, post-activity polypnea, weight loss, anosmia, joint pain, palpitation, red eyes, intermittent fever
P43	Male	7	Phagocyte defect	EFL-1 defect	Scoliosis, short stature, chronic diarrhea, retinitis pigmentosa	Asymptomatic	Asymptomatic	No	No	None	None	Recovered	None
P44	Female	1	Innate immune defect	IL-12 receptor defect	Bcgitis	Fever	Mild	Yes, other indication	No	None	None	Recovered	None
P45	Male	9	Innate immune defect	NBAS deficiency	Intermittent neutropenia and thrombocytopenia, growth retardation, hypothyroidism, atelectasis	Fever, sore throat, cough, dyspnea	Critical	Yes	Yes	Favipiravir, IVIG, Remdesevir, convalescent plasma, enoxoparin, Steroids	MV	Twice COVID-19 infection, died	-
P46	Female	4 months	Autoinflammatory disorder	LIPIN2 mutation (Majeed Syndrome)	Neutropenia, anemia	Fever, dyspnea	Critical	Yes	Yes	Steroids, remdesevir, Tocilizumab, surfactant, Plasmapheresis, etoposide, Antibiotherapy	MV	Persistent COVID-19 infection, died	-
P47	Female	11	Autoinflammatory disorder	ADAM 17 deficiency	Mucocutaneous candidiasis, PFO	Fever, sore throat, cough,	Moderate	Yes	No	Favipravir	Mask O2	Recovered	None

APECED (APS-1): autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, **CID:** combined immunodeficiency, **CVID:** common variable immunodeficiency, **IBD:** inflammatory bowel disease, **ICF:** immunodeficiency–centromeric region instability–facial anomalies syndrome, **MV:** mechanical ventilation, **NIV:** non-invasive ventilation, **PAD:** predominantly antibody deficiency, **PDA:** patent ductus arteriosus, **PFO:** patent foramen ovale, **VSD:** ventricular septal defect, **WAS:** Wiskott–Aldrich syndrome.

DISCUSSION

Since the pandemic started, there have been numerous publications on COVID-19 in IEI patients. These publications include summaries of one or more cases, lists of SARS-CoV-2 infections found in specific centers or nations, and presentations of data gathered for international projects (2,11,16,17). Some of them were meta-analyses (10,18). A large portion of the content was specific to adult patients and only a few publications exclusively concerned children (19,20).

Here, we report on pediatric IEI patients who had undergone HSCT and were diagnosed with SARS-CoV-2 infection, summarizing their clinical course, long-term outcomes, and factors associated with severe or critical COVID-19.

Unlike Shields et al. and Goudouris et al., male patients dominated the study group, similar to Meyts et al., Aydıner et al., and Marcus et al. (2,5-7,21). Our cohort is mostly pediatric, hence the median age was 8.5 years old, which is younger than many previous studies (2,5,9).

While CIDs were the most common IEI group in our study, PADs, which were the second most common, are the most common in many other studies (2,6,18). Similar to our study, the study by Aydıner et al. from Turkey found that the most common IEI group was CID (7). A possible explanation for this is that CIDs are more common in Turkey than in many other countries.

Most of the patients in our study were managed at home without hospital care. The hospitalization rate was significantly lower than the international cohorts published by the Mexican, the Iranian, and the UK groups, while similar to the Italian, Brazilian, and Spanish cohorts (5,6,8,9,20,22). The highest hospitalization rate was found in CIDs, as reported by Aydıner et al (7).

Our hospitalized patients had at least one comorbidity. COVID-19 severity was linked to comorbidities, notably chronic lung disease. Hospitalization rate and severity were related to chronic pulmonary illness in our group, as in the literature (6).

Immunoglobulin usage was associated with severe COVID-19. A plausible explanation for this finding is that 33/44 patients with comorbidities received IVIG, in line with Goudouris et al (5). This may be linked to the observation that all severe COVID-19 infections in patients undergoing IVIG exhibited reduced IgA levels.

The effects of immunosuppressive usage on disease severity are controversial. Immunosuppressors have been shown in some trials to be ineffective (23), to increase the risk of serious infection (24), and to have a protective effect by decreasing the inflammatory process (5). In our study, immunosuppressor usage was a non-interfering factor for COVID-19.

In our cohort, 8% were asymptomatic, while 61% developed mild symptoms. The asymptomatic patients' ratio was similar to some previous studies (2,5,6), while lower compared to Italian (5), Spanish (22) and Iranian (20) cohorts when the mild symptomatic patients ratio was higher. In our institution, parents reach our team by phone call if they have experienced symptoms such as fever, respiratory symptoms, gastrointestinal manifestations, malaise, or any exacerbation of their preexisting symptoms, in order to reduce transmission. Any patient with at least one of the above-mentioned complaints was referred to the hospital for further evaluation. In addition, our registered patients who had routine follow-up and had received monthly IVIG administrations were also checked for any infection signs and symptoms. This could result in a higher rate of COVID-19 diagnosis with mild symptoms. The leading symptoms at admission in our cohort were fever, cough, and dyspnea, consistent with those observed in other cohorts (5,7,9,25).

We observed persistent or prolonged COVID-19 infection in two IEI patients—one with ICOS deficiency and one with LPIN2 deficiency (Majeed syndrome). Relapsing–remitting COVID-19 occurred in six IEI patients, including those with incomplete DiGeorge syndrome (DGS), NBAS deficiency, Bruton agammaglobulinemia, TACI deficiency, NFKB2 deficiency, DIAPH1 deficiency, and in a post-HSCT patient with PNP deficiency who lacked B-cell engraftment. These patients all had B lymphopenia and/or humoral immune system defect, and all but one (DIAPH1-moderate) were classified as severe-critical. This supports the findings of prior research in the literature, which indicate that chronic or relapsing-remitting infection is linked to profound humoral immunodeficiency and the inability to generate new antibody responses to COVID-19 (10,26,27).

In the current COVID-19 pandemic, investigators demonstrated that if initial IFN responses are defective, SARS-CoV-2 replicates without control, spreads from

the upper airways to the lungs and other tissues, and inflammation exacerbates due to exaggerated immune cell recruitment (28,29). Pablo et al. identified that the expression levels of LPIN2 in blood samples from COVID-19 patients clearly distinguish symptomatic from asymptomatic patients. There is an inverse correlation between the expression of LPIN2 and the levels of inflammatory and damage-related factors such as IL6, VEGF, and CCl3. Their analyses of databases from COVID-19 patients show that LPIN2 expression levels negatively correlate with the severity of the disease (30). Our patient with LPIN2 deficiency, COVID-19 infection progressed very rapidly, and inflammatory markers such as CRP, ferritin, and IL-6 were extremely high. Our patient's condition concurs with this literature as well.

In our cohort, a patient with NBAS deficiency had one of the most severe conditions, longer viral shedding, and passed away. In the Italian cohort, one patient with NBAS deficiency was also hospitalized; symptoms were prolonged till four weeks and the patient recovered (9). Our patient initially had chronic lung disease, which required hospitalization and PICU admission prior to COVID-19. Despite multidisciplinary approaches, he died from multiple organ failure. NBAS deficiency is an IEI in a group of innate immune defects. In the literature, innate immune defects have considerably higher ICU admission and mortality rates (18). In addition, one study indicated NBAS-related functions might be important for early SARS-CoV-2 infection response (31).

Studies have shown that individuals with CID are at increased risk for severe COVID-19 outcomes, including a substantially higher mortality rate. Moreover, patients with CID who have received curative treatments such as gene therapy and HSCT demonstrate a more favorable clinical trajectory (18). In our study, CID patients who underwent HSCT exhibited a favorable outcome and remained alive post-COVID-19, consistent with the literature.

This cohort had an overall mortality rate of 4%, and all deaths were early in the pandemic. Other studies had similar findings to our cohort, where patients through different phases of the pandemic experienced a mild clinical course with limited symptoms (9,17). Higher mortality in previous studies may be explained by differences in viral strains, vaccination, and changes in treatment modalities, such as the widespread use of monoclonal antibodies.

Remdesivir and convalescent plasma were applied to 2 patients with persistent infection and 3 patients with relapsing-remitting infection. One persistent case recovered, and one died due to MIS-C. Two patients with COVID-19 recovered, and one recovered in the first episode of infection but died in the second. In the literature, consistent with our study, long-term multiple remdesivir courses have been shown to be effective in persistent SARS-CoV-2 infection in humoral immune defects (32-34). As in our study, many studies have shown that convalescent plasma may be effective for uncontrolled or prolonged infection with SARS-CoV-2, especially in patients with impaired humoral immunity. Regrettably, the utilization of monoclonal antibody therapy, which was the widely accepted treatment during the advanced phases of the pandemic, was not feasible for our patients. In countries with limited access to monoclonal antibody therapies, convalescent plasma is a valuable option.

Quinti et al. found that patients with agammaglobulinaemia had a mild course of COVID-19, while patients with CVID had a more severe form of the disease (10). Another study demonstrated in a murine model that B cell lymphopenia induces a natural decrease in germinal center IL-6 activation, hence conferring protection against systemic autoimmunity (35). In our study, COVID-19 severity varied substantially across different B-cell–related IEIs. Patients with agammaglobulinemia have been reported to show heterogeneous clinical courses, and this pattern was also evident in our cohort, where two had mild disease, three had moderate disease, and one experienced critical illness. In contrast, among patients with CVID, three of four experienced moderate COVID-19, whereas one had a mild presentation. A broader range of clinical outcomes was also observed in patients with B-cell lymphopenia, spanning from asymptomatic infection to critical disease. Taken together, these findings indicate that neither agammaglobulinemia nor other forms of B-cell deficiency consistently confer protection against COVID-19–related inflammation. Instead, our results align with emerging evidence suggesting that B-cell defects may predispose certain patients to prolonged or relapsing infection rather than mitigating disease severity.

In our study, the outcome of COVID-19 was less severe in patients who had undergone HSCT, particularly in those infected more than 100 days after transplantation. Two patients developed severe disease. The first patient, who had NIK deficiency, was eight years post-HSCT, had

bronchiectasis, was receiving IVIG therapy, had rheumatoid arthritis treated with colchicine, and lacked secondary lymphoid organs. The second patient, who had PNP deficiency, was 16 years post-HSCT, had no B-cell engraftment, and was also receiving IVIG therapy. A cohort study involving 318 HSCT recipients, only four of whom had IEIs, reported that COVID-19 may present more severely during the first 100 days after transplantation. In contrast, in our study, the two patients who developed COVID-19 within the first 100 days post-HSCT recovered with only mild symptoms (36). In another study involving 247 HSCT recipients, 10 of whom had IEIs, a substantial proportion of patients were hospitalized and monitored but ultimately recovered from COVID-19 with mild symptoms and without the need for specific antiviral therapy. Similarly, in our study, most HSCT patients recovered from COVID-19 with mild symptoms and without sequelae (37)

Long-term follow-up studies in IEI patients have shown that fatigue is the most prevalent post-COVID-19 symptom and is not associated with illness severity, consistent with findings in the general population. Similarly, in our cohort, fatigue was the most common long-term complaint and showed no association with the severity of the initial infection (12,13).

CONCLUSION

In summary, this study provides an analysis of the clinical progression, final outcome, and long-term side effects of SARS-CoV-2 infection in a significant cohort of pediatric patients with IEI identified over a long surveillance period. The severity and mortality of COVID-19 in this cohort appear to be associated with a higher prevalence of comorbidities, particularly chronic lung disease. Disease severity was highly variable across IEI groups and was particularly associated with innate immune system defects, autoinflammatory disorders, and humoral immune defects. We also confirmed that in some cases patients with humoral immunodeficiency may develop persistent or relapsing infection. Our study may justify the recommendation to use convalescent plasma and remdesivir for COVID-19, especially for patients with humoral immune defects, B-cell lymphopenia, and preexisting comorbidities. In addition, our study demonstrated that pediatric patients with inborn errors of immunity who underwent HSCT generally experienced a favorable clinical course and mild long-term effects following COVID-19 infection.

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There is nothing to disclose

Ethical Approval

The Ankara University Faculty of Medicine Clinical Trials Ethics Committee approved this study for with protocol number 2024/232.

Author Contributions

Concept: **Nazlı Deveci, Sule Haskaloglu, Figen Dogu,** Design: **Nazlı Deveci,** Data collection or processing: **Nazlı Deveci,** Analysis or Interpretation: **Nazlı Deveci,** Literature search: **Nazlı Deveci,** Writing: **Nazlı Deveci,** Approval: **Nazlı Deveci.**

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