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Genetic and immunologic evaluation of children with inborn errors of immunity and severe or critical COVID-19

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Background: Most severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected individuals are asymptomatic or only exhibit mild disease. In about 10% of cases, the infection leads to hypoxemic pneumonia, although it is much more rare in children.

Objective: We evaluated 31 young patients aged 0.5 to 19 years who had preexisting inborn errors of immunity (IEI) but lacked a molecular diagnosis and were later diagnosed with coronavirus disease 2019 (COVID-19) complications.

Methods: Genetic evaluation by whole-exome sequencing was performed in all patients. SARS-CoV-2–specific antibodies, autoantibodies against type I IFN (IFN-I), and inflammatory factors in plasma were measured. We also reviewed COVID-19 disease severity/outcome in reported IEI patients.

Results: A potential genetic cause of the IEI was identified in 28 patients (90.3%), including mutations that may affect IFN signaling, T- and B-cell function, the inflammasome, and the complement system. From tested patients 65.5% had detectable virus-specific antibodies, and 6.8% had autoantibodies neutralizing IFN-I. Five patients (16.1%) fulfilled the diagnostic criteria of multisystem inflammatory syndrome in children. Eleven patients (35.4%) died of COVID-19 complications. All together, at least 381 IEI children with COVID-19 have been reported in the literature to date. Although many patients with asymptomatic or mild disease may not have been reported, severe presentation of COVID-19 was observed in 23.6% of the published cases, and the mortality rate was 8.7%.

Conclusions: Young patients with preexisting IEI may have higher mortality than children without IEI when infected with SARS-CoV-2. Elucidating the genetic basis of IEI patients with severe/critical COVID-19 may help to develop better strategies for prevention and treatment of severe COVID-19 disease and

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected children normally show no or mild disease and constitute only a small proportion of patients with coronavirus disease 2019 (COVID-19).[1-3] Thus, few children are hospitalized (because of less severe symptoms and signs), as life-threatening complications are rare unless the children have underlying medical conditions,[4] including specific types of inborn errors of immunity (IEI).[5] Nevertheless, a rare postinfectious phenomenon referred to as multisystem inflammatory syndrome has been described in children (MIS-C) and is thought to be due to an unknown pathogenic mechanism.[6] The main hypothetical explanations for the generally milder infection in children are a less aggressive immune response triggered in children compared to that in adults, proper type I IFN (IFN-I) baseline levels, higher functional number of plasmacytoid dendritic cells, and/or higher baseline cross-reactive immunity as a result of the frequent exposure to other respiratory tract infections during childhood.[5,7,8] The recently emerging Omicron variant has, however, increased the number of coronavirus hospitalizations in unvaccinated children.[9]

The impact of SARS-CoV-2 infection on patients with different types of IEI is currently debated[5] because patients with some IEI entities show critical COVID-19 conditions, whereas other groups of IEI patients are asymptomatic or only present with mild manifestations after infection. Although the exposure to pathogens may be lower in IEI patients as a result of a stricter self-isolation, it should be noted that a majority visit the hospital and medical centers regularly, which may still expose them to different pathogens, including SARS-CoV-2. In addition to the aberrant immune response, the majority of IEI patients have infectious or noninfectious pulmonary complications before SARS-CoV-2 infection. The pulmonary lesions may thus underlie the poor outcomes after SARS-CoV-2 infection in these patients.

Our prospective epidemiological study on IEI patients in the Iranian national registry showed that although there was only a 1.23-fold higher incidence of infection compared to the general population (19 of 2754 live patients in October 2020), these patients experienced a 10-fold higher COVID-19–related mortality, mainly in patients with combined immunodeficiency (CID) or immune dysregulation.[10] In contrast, antibody-deficient patients showed a lower fatality rate unless they had concomitant chronic lung diseases.[11,12] In a report of 582 children and adolescents in Europe with PCR-confirmed SARS-CoV-2 infection, only 3 patients (0.5%) had a previously diagnosed IEI.[13] In contrast, immunologic complications underlie 7.4% to 12.5% of COVID-19 patients admitted to pediatric emergency departments.[14] In a recent multinational cohort of 94 IEI patients reported by the European Society for Immunodeficiencies, which mainly included antibody deficiency patients, a 9.5% mortality rate and a comparatively better outcome of COVID-19 in CID patients who had undergone hematopoietic stem-cell transplantation were noted.[15]

The literature on reported IEI patients with COVID-19 indicates that although some of the most prevalent forms of IEI (caused by mutations in *BTK, SERPING1,* and *CYBB*) show a high number of infected individuals, they mainly presented with mild-moderate diseases. Furthermore, patients with mutations in *ATM* or *TACI* seemingly display a very low susceptibility to severe COVID-19.[16-19] Rare monogenic mutations involving the Toll-like receptor (TLR) and IFN pathways were enriched in patients with severe and critical COVID-19.[16,19-26] Autoantibody against IFN-I (an IEI phenocopy) has furthermore been shown to be a major underlying cause of mortality in COVID-19 patients, especially in elderly individuals.[22,23]

To further investigate the impact of SARS-CoV-2 infection in different types of IEI patients and to identify the genetic basis of severe forms of the disease, we evaluated the immunologic profile and genetic characteristics of young IEI patients in our immunodeficiency registry who had severe or critical forms of infection, including hypoxemic pneumonia and MIS-C.

Abbreviations used

ACMG:	American College of Medical Genetics and Genomics
CID:	Combined immunodeficiency
COVID-19:	Coronavirus disease 2019
HRCT:	High-resolution computed tomography
ICU:	Intensive care unit
IEI:	Inborn errors of immunity
IFN-I:	Type I IFN
IUIS:	International Union of Immunologic Societies
KD:	Kawasaki disease
MIS-C:	Multisystem inflammatory syndrome in children
NF-κB:	Nuclear factor kappa–light-chain enhancer of activated B cells
PAD:	Predominantly antibody deficiencies
RBD:	Receptor binding domain
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2
TLR:	Toll-like receptor
WES:	Whole-exome sequencing

METHODS

Patients and clinical evaluation

This study was conducted on severe or critically ill young COVID-19 IEI patients, prospectively enrolled onto the national IEI registry in Iran[27,28] during August-September 2020. Considering the inclusion time (before the wave of a new variant of concern in November 2020), patients included in the study were infected by wild-type SARS-CoV-2 virus and unvaccinated. IEI patients were diagnosed by clinical immunologists according to national guidelines[29] and standard laboratory tests for clinical and immunologic evaluations.[27,28] Subsequently, patients with a suspected diagnosis were referred and reevaluated in the Children's Medical Center for a defined clinical diagnosis according to the criteria of the European Society for Immunodeficiencies.[30]

During the sample collection period, Iran had a population of 84,012,567 citizens (with an average annual birthrate of 1,300,000), and COVID-19 was reported in 532,492 patients (incidence of 2052 cases per day, 10.3% with a severe or critical condition, and a 3.5% mortality rate; www.worldometers.info/coronavirus/, reported by the Iranian Ministry of Health, Tehran, Iran, access data November 2020). At this time, severe and critical cases were reported only in 0.2% of the infected children, and mortality was only observed in 0.004%. Strengthening the Reporting of Observational Studies in Epidemiology was used for the observational cohort study. Severe cases were defined on the basis of the revised World Health Organization criteria as SpO_2 < 90% on room air at sea level, increased respiratory rate (>30 breaths/min in children >5 years old; ≥40 in children 1-5 years old; ≥50 in

children 2-11 months old; and ≥60 in children <2 months old) and signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).[31] Critical cases occurred in individuals who were admitted to the intensive care unit (ICU) for respiratory failure, septic shock, and/or multiple organ dysfunction.[32] MIS-C was diagnosed on the basis of World Health Organization criteria,[33] and all cases were confirmed by echocardiography, which demonstrated dilated coronary arteries (Z score above 2.5 indicating dilation according to American Heart Association classification).[34,35]

This study received approval from the ethics committee of the Tehran University of Medical Science. Moreover, written informed consent was obtained from all patients and/or their parents or legal guardians. All except 1 patient had a clinical diagnosis of IEI before the time of COVID-19, and high-resolution computed tomography (HRCT) and reverse transcriptase PCR, as well as complete blood count, C-reactive protein, and erythrocyte sedimentation rate, were evaluated in these patients. For the remaining single patient with a clinical diagnosis of IEI at the same time of COVID-19 diagnosis, a comprehensive questionnaire was provided and filled out consisting of demographic data, clinical manifestations related to IEI and COVID-19, and laboratory test findings relevant for diagnosis of both IEI and COVID-19. Furthermore, the clinical outcome was also documented for each patient. Blood samples were collected during 48 hours after the presentation of severe or critical manifestations (ICU admission).

Genetic analysis and diagnoses in IEI patients with COVID-19

Genomic DNA was extracted from whole blood of the patients, and whole-exome sequencing (WES) was performed using a previously described pipeline.[36,37] Candidate variants were evaluated by the Combined Annotation Dependent Depletion algorithm, and an individual gene given by using the Mutation Significance Cutoff was considered for impact predictions.[38] The pathogenicity of all disease-attributable gene variants was reevaluated using the updated guideline for interpretation of molecular sequencing by the American College of Medical Genetics and Genomics (ACMG) criteria,[39,40] considering the allele frequency in the population, computational data, immunologic data, and clinical phenotyping. Genetic changes in known IEI genes with a complete inheritance pattern and fulfilling the ACMG criteria were assigned as the main potential genetic cause, and other gene variants within antiviral immunity pathways with unknown significance in the ACMG criteria and/or incomplete inheritance patterns were referred to as potential modifiers.

To identify novel IEI-modifying genes, comparative enrichment analysis was performed between the severe/critical COVID-19 IEI patient cohort and the other 59 cases in unsolved IEI patients who had not been infected by SARS-CoV-2 or who had asymptomatic infection. These patients were from the same population and were followed every month during the first 16 months of the pandemic.[36,37] In this analysis, only genes that are mutated exclusively and/or recurrently (in at least in 3 cases) in our IEI cohort were considered. Furthermore, similar comparative enrichment analysis was performed by including an independent control cohort, which includes WES data from published mild/asymptomatic SARS-CoV-2–infected individuals (n = 288).[41-44] Reactome pathway enrichment analysis (reactome.org) was performed for functional enrichment analyses with the shared genes.

Classification of IEI patients

IEI patients were classified according to their clinical characteristics and immunologic evaluation, according to the International Union of Immunologic Societies (IUIS) updated classification: nonsyndromic CID or CID, combined immunodeficiencies with associated or syndromic features (syndromic CID), predominantly antibody deficiencies (PAD), diseases of immune dysregulation, congenital defects of phagocyte number or function (phagocytic disorders), autoinflammatory disorders, defects in intrinsic and innate immunity, complement deficiencies, and phenocopies of IEI.[45]

Inflammatory markers profiling in plasma of IEI patients

Inflammatory markers were analyzed in plasma samples using a multiplex proximity extension assay (Olink Inflammation panel kit, Olink Bioscience, Uppsala, Sweden).[46] This assay provides a microtiter plate for measuring 92 protein biomarkers, and each well contains 96 pairs of DNA-labeled antibody probes. When pairs of antibodies bind their target protein and are thereby brought in proximity, the DNA oligos are allowed to hybridize and to be extended, which creates double-stranded DNA molecules encoding the identity of the antibody pairs that can be detected by real-time PCR. The inflammatory profile of IEI patients was compared to age-matched healthy controls as well as with patients with mild COVID-19, severe COVID-19, and MIS-C published previously.[47,48]

Detection of SARS-CoV-2–specific antibodies and autoantibody screening in IEI patients

Plasma samples were tested for the presence of anti-spike (anti-S1/S2) and anti–receptor binding domain (anti-RBD) antibodies levels using an in-house enzyme-linked immunosorbent assay described previously (positive defined as being above the cutoff of prepandemic samples collected from healthy individuals).[16,35,49,50] Plasma samples were also screened for autoantibodies against 14 IFNs and 10 related cytokines using a bead array, as described in detail previously,[16,35,49,50] using recombinant human proteins coupled to magnetic beads (MagPlex, Luminex, Austin, Tex) containing different fluorescence markers. Serum from a patient with autoimmune polyendocrine syndrome type 1 due to a homozygous loss-of-function *AIRE* mutation and known autoantibody reactivity against IFN-I was included as a positive control, as well as sera from 98 healthy blood donors as negative controls. The neutralizing activity of anti-IFN autoantibodies in positive samples was evaluated with a reporter luciferase activity as described previously.[35] Autoantibodies related to systemic autoimmune rheumatic diseases were tested in patients during the severe/critical COVID-19 admission, including rheumatoid factor, anti–double-stranded DNA, anti-nuclear antibodies, and anti-neutrophil cytoplasmic autoantibodies.[51]

Literature search strategy for reported IEI patients with COVID-19

Literature searches for IEI patients with COVID-19 reported up to August 2022 were conducted of the PubMed, Web of Science, and Scopus databases, applying the following keywords: “inborn errors of immunity” OR its synonyms (“IEI” OR “primary immunodeficiency*” OR “primary immune deficiency*” OR “PID”) in combination with terms for “COVID-19” presentation (including “Covid*” OR “SARS-CoV-2” OR “coronavirus”). Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) was used as the guideline for the systematic review section. The articles were first screened by title and abstract to exclude all irrelevant studies, and then full text was assessed for eligibility criteria (written in English, conducted on human subjects, reporting at least 1 IEI patient with COVID-19, without secondary immunodeficiency, and with detailed description of genetic, clinical, and immunologic features). Studies on the immune response against vaccination in IEI patients were not included. A manual search of bibliographies of the retrieved publications was performed to identify additional relevant studies. All previously reported IEI cases were categorized into 2 groups according to the defined molecular diagnosis underlying IEI, as follows: group I, only clinically diagnosed, and group II, both clinically and genetically diagnosed.

Statistical analysis

Different parameters between patient groups were compared. One-sample Kolmogorov-Smirnov test was applied to estimate whether the data distribution was normal. Parametric and nonparametric analyses were performed according to the findings of this evaluation. Statistical analysis was performed

TABLE I. Demographic data and clinical diagnosis of 31 IEI patients with severe/critical COVID-19

Patient ID	Sex	Age	Clinical IEI diagnosis	Consanguinity	Treatment before COVID-19	COVID-19 condition	Other treatment during COVID-19	Outcome
P1	M	8y	Hyper-IgM syndrome	Yes	IVIG + PAb + TAb	ICU admission	IVIG + TAb + Co + Asp + AP + PN	Survived
P2	F	13y	Immune dysregulation		TAb + Bio	ICU admission	Tab + Bio + Co + PN	Survived
P3	M	18y	Immune dysregulation	Yes	TAb + Bio + Co + IS	ICU admission	TAb + AP + PN	Survived
P4	M	15y	Innate immunodeficiency		PAb + TAb	MIS-C; ICU admission	IVIG + TAb + Ace + AP + PN	Survived
P5	F	10y	CID		IVIG + PAb + TAb	IFN Auto-Ab; ICU admission	IVIG + TAb + Ace + Bio + PN + CPR + CoP	Died
P6	M	9y	CID	Yes	IVIG + PAb + TAb	ICU admission	IVIG + TAb + PN + CoP	Survived
P7	M	2y	Innate immunodeficiency		PAb + TAb	MIS-C; ICU admission	IVIG + TAb + Ace + Bio + AP + PN	Survived
P8	M	16y	Immune dysregulation		TAb + Bio	ICU admission	TAb + Bio + Co + PN	Survived
P9	M	16y	Immune dysregulation		TAb + Bio	Hospital admission, O2/NIV	TAb + Bio + Co	Survived
P10	M	15y	CID		IVIG + TAb + Bio	ICU admission	IVIG + TAb + PN + CoP	Survived
P11	M	11y	CID		TAb + Bio	ICU admission	IVIG + TAb + AP + ACEI + AMI + PN + CoP + CPR	Died
P12	F	16y	Innate immunodeficiency	Yes	TAb	ICU admission	TAb + PN + Co	Survived
P13	M	19y	autoinflammatory disorders		TAb + Bio + Co + IS	ICU admission	TAb + Co + AP + PN	Survived
P14	M	10y	CID	Yes	IVIG + TAb	ICU admission	IVIG + TAb + Co + AP + ACEI + AMI + PN + CPR	Died
P15	F	17y	Immune dysregulation		TAb + Bio	ICU admission	TAb + AP + PN	Survived
P16	M	10y	Innate immunodeficiency	Yes	TAb	ICU admission	TAb + Bio + PN	Survived
P17	M	15y	Autoinflammatory disorders	Yes	TAb + Bio	Hospital Admission, O2/NIV	TAb + Co	Survived
P18	M	7y	CID	Yes	IVIG + Tab + Co + Bio	ICU admission	IVIG + TAb + AP + ACEI + AMI + PN + CPR	Died
P19	F	3y	Innate immunodeficiency	Yes	Tab	MIS-C; ICU admission	IVIG + Tab + Ace + Bio + AP + ACEI + AMI + PN + CPR	Died
P20*	M	5m	SCID	Yes	—*	ICU admission	TAb + IVIG + vitamin B6 + Co + PN + CPR	Died
P21	M	12y	Immune dysregulation		TAb + Bio + Co	ICU admission	TAb + Co + PN	Survived
P22	F	10y	Innate immunodeficiency		Tab	Hospital admission, O2/NIV	TAb + Bio	Survived
P23	M	16y	Immune dysregulation		IVIG + TAb + Bio	IFN Auto-Ab ICU admission	IVIG + TAb + Co + AP + PN	Survived
P24	M	13y	Autoinflammatory disorders	Yes	IVIG + TAb + Bio + Co	Hospital admission, O2/NIV	IVIG + Tab	Survived
P25	M	9y	CID		IVIG + TAb + Bio	ICU admission	IVIG + TAb + AP + ACEI + AMI + PN + CPR	Died
P26	M	11y	Innate immunodeficiency		TAb + Bio	MIS-C; ICU admission	IVIG + TAb + Ace + Bio + AP + PN + CPR	Died
P27	M	15y	Innate immunodeficiency		PAb + TAb + Bio	MIS-C; ICU admission	IVIG + TAb + Ace + Bio + AP + PN	Survived
P28	M	2y	SCID/CID	Yes	IVIG + PAb + TAb	ICU admission	IVIG + TAb + AP + ACEI + AMI + PN + CPR	Died
P29	M	13y	Agammaglobulinemia	Yes	IVIG + PAb + TAb	Hospital admission, O2/NIV	IVIG + TAb + Bio + PN + CoP	Survived

(Continued)

TABLE I. *(Continued)*

Patient ID	Sex	Age	Clinical IEI diagnosis	Consanguinity	Treatment before COVID-19	COVID-19 condition	Other treatment during COVID-19	Outcome
P30†	M	2y	SCID	Yes	IVIG + PAb + TAb	ICU admission	IVIG + TAb + PN + CPR	Died
P31†	M	10y	Immune dysregulation	Yes	TAb + Bio + Co	ICU admission	TAb + Co + AP + ACEI + AMI + PN + CPR	Died

Ace, Acetaminophen; *ACEI,* angiotensin-converting enzyme inhibitors; *AMI,* amiodarone; *AP,* antiplatelet or clopidogrel; *Bio,* Biological agents or nonsteroidal anti-inflammatory drugs; *Co,* Corticosteroids (not 3 months before COVID-19); *CoP,* Convalescent plasma; *CPR,* Cardiopulmonary resuscitation; *IFN Auto-Ab,* positive for autoantibody against IFN-I; *IS,* immunosuppressants (not 3 months before COVID-19); *IVIG,* Intravenous immunoglobulin; *NA,* plasma not available for immunologic assays; *NIV,* Noninvasive ventilation; *PAb,* prophylactic antibiotics; *PN,* parenteral nutrition; *SCID,* Severe CID; *TAb,* therapeutic antibiotic.
*Patient with clinical diagnosis of IEI at the same time with COVID-19.
†Patients without available plasma samples for specific antibody/autoantibody tests.

by SPSS 21.0.0 (IBM, Armonk, NY) and R 3.4.1 (R Project; www.r-project.org). $P \leq .05$ was considered statistically significant.

RESULTS

Thirty-one IEI patients (6 female and 25 male) with a median age of 12 years (range, 5 months to 19 years) at the time of severe/critical COVID-19 were included in the study. Only 1 patient was above the age of 18 (P13, 19 years, Table I). On the basis of clinical and immunologic evaluation, we identified PAD (n = 2), CID (n = 10), autoinflammatory disorders (n = 3), diseases of immune dysregulation (n = 8), and innate immunodeficiencies (n = 8) (Fig 1, *A*). The diagnosis of IEI was made before the SARS-CoV-2 infection (except for 1 patient who had severe CID and COVID-19 diagnosed at the same time; P20, Table I). Parental consanguinity was noted in 15 patients (48.3%, Table I). Median age at the time of the study was similar in all IEI groups, except for patients with immune dysregulation who had a significantly older age compared to patients with CID (16.0 vs 9.0 years, respectively, $P = .021$).

The majority of patients were admitted into the ICU (n = 26, 83.8%). COVID-19–associated features were mainly shortness of breath (n = 29, 93.5%), cough (n = 27, 87.0%), and fever (n = 26, 83.8%). Details of the remaining clinical presentations associated with the SARS-CoV-2 infection are summarized in Fig E1 in this article's Online Repository available at www.jacionline.org. An increased respiratory frequency was recorded in 20 patients (64.5%), blood oxygen saturation of ≤90% in 17 (54.8%), and a PaO_2/FiO_2 ratio of <300 in 8 patients (25.8%). Lung infiltrates >50% documented by computed tomographic imaging were observed in 22 (70.9%), ground-glass pattern in 27 (87.0%), crazy paving in 11 (superimposed interlobular septal thickening and intralobular septal thickening, 35.4%), and coronary artery dilatation in 5 (16.1%). Of note, a selected group of patients also presented with dermatologic lesions, peripheral extremity changes (including diffuse erythema, indurative edema, and periungual desquamation), and cardiovascular lesions (n = 5, 16.1%, Fig E1). These 5 patients fulfilled the diagnostic criteria of MIS-C[52] (P4, P7, P19, P26, P27) (Table I). None of the surviving patients manifested long COVID-19 manifestations. At the end point of this study, 11 patients (35.4%; including 2 with MIS-C) had died of infectious complications, potentially reflecting a slight improvement in the management of IEI patients compared to our previous report,[10] but still showing a 3000-fold higher mortality rate compared to the COVID-19 death rate in normal children (~0.01%).[13,53] Given that preexisting lung involvement is a risk factor for more severe SARS-CoV-2 infection, we correlated the outcome of COVID-19 disease with the previous HRCT imaging data in selected patients. HRCT was medically indicated in 18 patients, and among these, 10 presented chronic lung involvement (including bronchiectasis, peribronchial thickening, mucous plugging, and interstitial lung diseases), mainly with a clinical diagnosis of CID (n = 7, 3 syndromic and 4 nonsyndromic CID, 70.0%). As expected, IEI patients with an abnormal HRCT before COVID-19 had a higher mortality rate compared to the remaining patients, but the difference was not statistically significant (60.0% vs 28.5%, $P = .20$). Parental consanguinity was observed in 70% of patients with abnormal HRCT, and 63.6% of the deceased patients, which was slightly higher than in patients without chronic lung damage (38%, $P = .09$) and surviving IEI patients (43.1%, $P = .21$), respectively.

WES was subsequently conducted in all patients, as none of them had a genetic diagnosis before this study. A total of 453 known IEI genes[45,52] with specific Mendelian inheritance were prioritized on the basis of the clinical diagnosis of the patients and the ACMG pathogenicity of the identified mutations. A potential genetic cause of the IEI was identified in 28 patients (90.3%), including genetic defects in the IFN pathway (*TLR7, TICAM1, IFNAR1*) (n = 3, 9.6%), T-cell development/epigenetic regulation (*IL7R, TBX1, DNMT3B, TERT, NOTCH1*) (n = 7, 22.5%), regulatory T-cell function (*BACH2, STXBP2*) (n = 3, 9.6%), B-cell development (*BTK, IKZF1, PIK3CD, NFKB1, SH3KBP1, UNG*) (n = 6, 19.3%), lymphocyte apoptosis pathway (*CASP10*) (n = 1, 3.2%), motility of phagocytes pathway (*CFTR*) (n = 1, 3.2%), inflammasome pathway (*NLRP1*) (n = 1, 3.2%), anti-inflammation pathway (*IL37*) (n = 1, 3.2%), and regulators of complement activation pathway (*CFH, CFHR1, PIGA*) (n = 5, 16.1%) (Fig 2 and Table II; and see Tables E1 and E2 in the Online Repository at www.jacionline.org). Among these patients, the patients with *TLR7* (P1) and *IFNAR1* (P19) mutation were recently included in a larger cohort of patients with *TLR7* mutation[16,54] or reported as a single case.[35] Parental consanguinity did not significantly affect the molecular diagnosis yield (93.7% vs 86.6%, $P = .50$).

We next identified potential modifying gene defects in the antivirus immunity–related pathways, including the IFN pathway, lymphocyte development/epigenetic regulation, DNA repair, IL-1/inflammasome activation, nuclear factor kappa–light-chain enhancer of activated B cells (NF-κB) activation, and autoinflammatory responses (Fig 2, Table II, and see Table E1 and Table E2

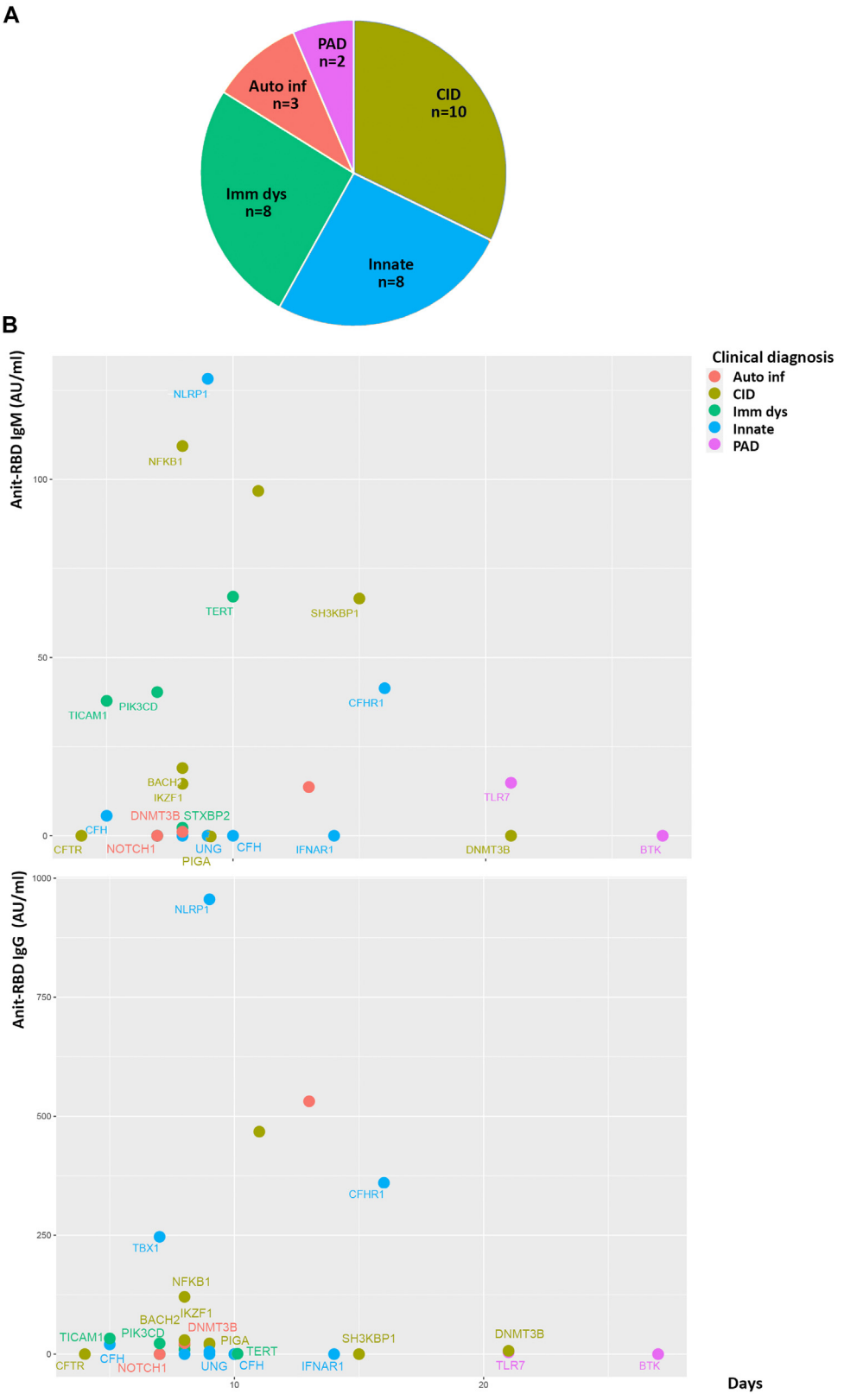

FIG 1. **(A)** Classification of IEI according to clinical diagnosis in 31 Iranian patients with severe or critical COVID-19. *Auto inf,* Autoinflammatory disorders; *Imm dys,* disease of immune dysregulation; *Innate,* innate immunodeficiency. **(B)** Correlation of specific IgG and IgM response against RBD of the spike protein in different categories of IEI patients. Genetic defects of solved IEI patients are depicted; color codes refer to clinical diagnosis of patients according to their initial immunologic profile.

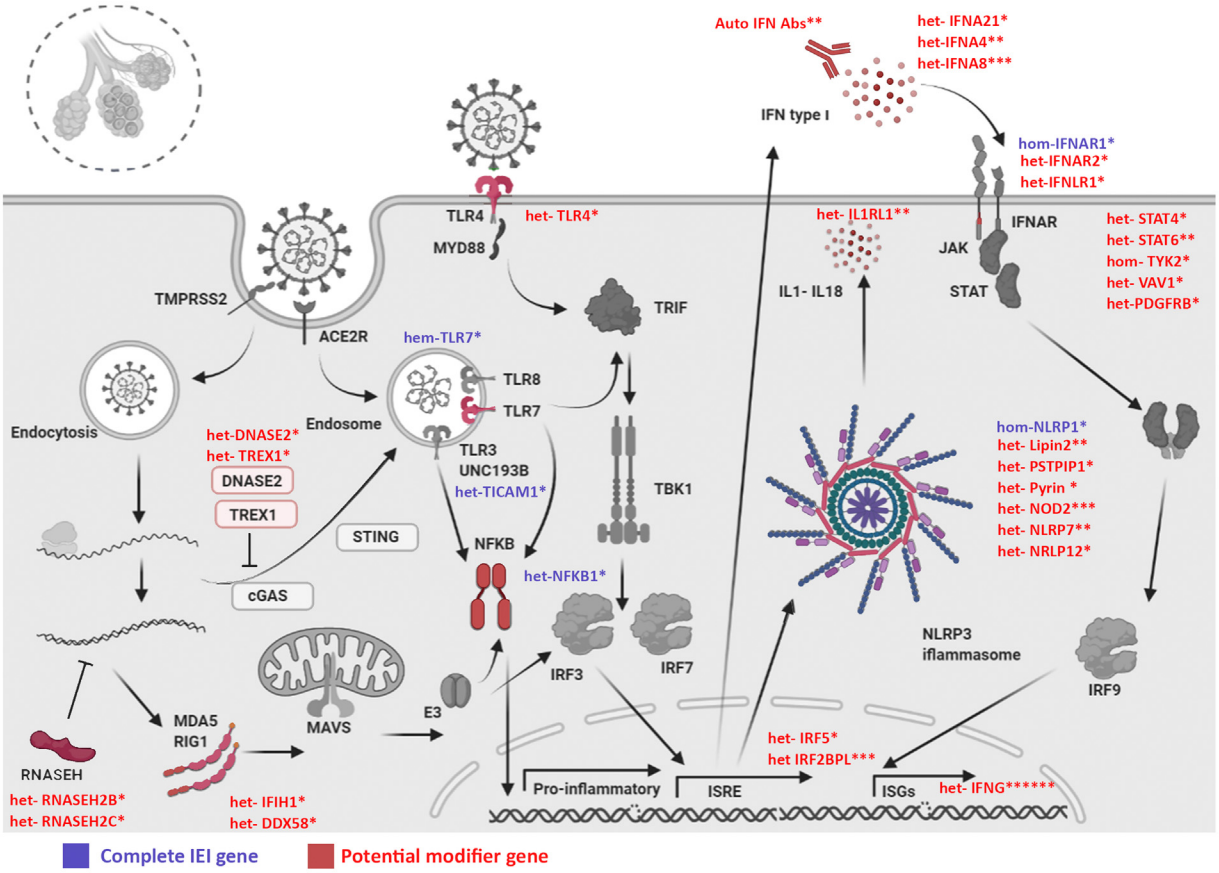

FIG 2. Extended SARS-CoV-2–related pathway analysis for evaluation of the impact of complete inheritance pattern *(purple)* and potential modifying gene defects *(red)* within the IFN pathway, IL-1/inflammasome activation, NF-κB activation, and autoinflammatory response pathways in a schematic presentation of the epithelial cell of lung alveoli or innate immune cells. *Asterisk* indicates one IEI patient. *Hem,* Hemizygous; *het,* heterozygous variants; *hom,* homozygous variants. Details of mutations are shown in Table II and Table E1 and Table E2.

in the Online Repository). By comparing the group of severe/critical COVID-19-IEI patients and unsolved IEI patients without COVID-19 (n = 30) or IEI patients with asymptomatic infection (n = 29) from the same population,[36,37] we observed an enrichment of deleterious variants in genes related to lymphocyte development/epigenetic regulation (n = 25, 80.6%, false discovery rate 1.74E-14, mainly in *KMT2D*), the inflammasome (n = 17, 54.8%, false discovery rate 4.24E-3, mainly in *NLRP1*) and the IFN pathway (n = 16, 51.6%, false discovery rate 5.23E-3, mainly in *IRF2BPL* and *IFNA8*).

We next performed a similar analysis on an independent control cohort, which consists of published WES of mild/asymptomatic non-IEI cases (n = 288).[41-44] Of note, regulation of cytokine production, innate immune response, and IFN-I were among the most significantly affected pathways in severe/critical COVID-19 patients with IEI (see Fig E2 in the Online Repository).

We also investigated the specific antibody responses against the RBD and S antigens in plasma collected on the second day after ICU admission/severe presentation in 29 cases (19 postive patients, 65.5%, median 8 days and range 4-27 days after initial presentation; Table III, Fig 1, *B*). Specific antibodies against RBD were observed in 17 patients (IgG in 14 patients, IgA in 9 patients, and IgM in 12 patients). Anti-S1/S2 antibodies were also detected in 18 patients (IgG in 14 patients, IgA in 10 patients, and IgM in 14 patients). Because most patients were admitted to the ICU less than 10 days after the onset of COVID-19, we tested whether the day of sampling would affect the outcome of the specific antibody responses. However, days of sample collection (from the onset of symptoms) were not significantly different between specific antibody-positive and -negative IEI patients (see Fig E3 in the Online Repository available at www.jacionline.org). Higher specific humoral immune responses in the early phase of infections were observed in several patients with immune dysregulation and innate immunodeficiency (Fig 1, *B*). As expected, most patients with negative specific antibody responses 20 days after disease onset were antibody deficient or patients with CID. However, some patients with immune dysregulation also presented with a lack of specific antibody production, which could be due to impaired humoral immunity in a subgroup of these patients, as previously suggested.[45]

Infectious disease susceptibilities in IEI patients are in some cases not due to the primary immune defect but instead mediated via autoantibodies against cytokines. Rheumatoid factor and antinuclear antibodies were positive in 5 (P9, P15, P23, P26, P27; 17.2%) and 3 (P2, P8, P9; 10.3%) cases, respectively, mainly in patients with immune dysregulation, whereas antineutrophil cytoplasmic autoantibodies and anti–double-stranded DNA

TABLE II. WES analysis of 31 IEI patients with severe/critical COVID-19

		Potential modifiers in antiviral immunity-related pathways					
Patient ID	**Main potential genetic cause of IEI**	**Lymphocyte development/ epigenetic**	**DNA repair gene defect**	**IFN pathway genes**	**IL-1 activation pathway genes**	**NF-κB pathway genes**	**Other related genes***
P1	*ATM* (hom)/; *TLR7* (hem)	*BCL11B* (het)		*IFNA4* (het)/*STAT6* (het)/; *IFIH1* (het)/ *RNASEH2C* (het)			*IL10RB* (het)/; *IL7R* (het)
P2	*CASP10* (het)	*SRP72* (het)		*IFNAR2* (het)			
P3	*NLRP1* (hom)	*KMT2D* (het)				*CARD14* (het)	*C3* (het)/; *IL11* (het)
P4	*CFH* (het)	*CLEC16A* (het)		*IRF5* (het)			*IL11* (het)/; *STX11* (het)
P5	*NFKB1* (het)	*SAMD9* (het)		*IFNA8* (het)			*NFAT5* (het)/; *C3* (het)/; *IL17RD* (het)/; *UNC13D* (het)
P6	*PIGA* (hem)			*IFNA8* (het)	*TNFRSF11A* (het)		*IL2RA* (het)
P7	*TBX1* (het)		*MSH6* (het)/ *MCM4* (het)/ *MCM10* (het)				*IL31RA* (het)
P8	*NOTCH1* (het)						*APOL1* (het)/; *IL17RC* (het)/*IL23R* (het)
P9	*TICAM1* (comp het)		*ATM* (het)	*RNASEH2B* (het)			*IL18R1(het)*/ *UNC13D* (het)
P10	*BACH2* (het)/ CASP10 (het)			*IFNA21* (het)/ *IFNA4* (het)	*NLRP1* (het)/ *NLRP2* (het)/; *IL1RL1* (het)		*CASP10* (het)/
P11	*CFTR* (comp het)	*KMT2D* (het)			*AP1S3* (het)		*IL10RA* (het)
P12	*BACH2* (het)			*DNASE2B* (het)	*MEFV* (het)		*IL8* (het)
P13	*NOTCH1* (het)					*PIK3CD* (het)	*IL31RA* (het)
P14	*SH3KBP1* (hom)	*BLK* (het)			*PSTPIP1* (het)	*NOD2* (het)	
P15	*TERT* (het)			*IRF2BPL* (het)	*NLRP2* (het)		*IL17RB* (het)
P16	*CFHR1* (hom)			*VAV1* (het)/; *IKZF2(het)*	*NCSTN* (het)		*C3* (het)/*IL17RE* (het)
P17	Not found	*PSEN1(het)*	*ATM* (het)		*NLRP1* (het)		*IL17RD* (het)
P18	Not found			*STAT4* (het)			*IL12RB2* (het)
P19	*IFNAR1* (hom)	*KMT2D* (het)		*TYK2* (hom)/; *PDGFRB* (het)	*NLRC4* (het)	*NOD2* (het)	*IL17C* (het)/ *IL4R* (het)/ *UNC13D* (het)
P20	*PIGA* (hem)	*TCF3* (het)					*IL2RA* (het)
P21	*STXBP2* (het)	*KMT2D* (het)	*ATM* (het)				*SRP72* (het)/; *IL12RB1* (het)/*IL17C* (het)/*IL27RA* (het)/*IL31RA* (het)/*UNC13D* (het)
P22	Not found	*KMT2D* (het)	*ERBB2IP* (het)		*PSTPIP1* (het)		
P23	*PIK3CD* (het)	*NOTCH1* (het)			*MAP3K6* (het)	*CARD14* (het)	*IL34* (het)/ *IL7R* (het)
P24	*DNMT3B* (hom)	*BCL11B* (het)		*DDX58* (het)/ *TREX1* (het)	*IL1RL2* (het)		*SAMD9* (het)
P25	*IKZF1* (het)	*CLEC16A* (het)		*IRF2BPL* (het)	*TNFRSF11A* (het)		*APOL1* (het)/ *IL16* (het)/; *IL24* (het)
P26	*CFH* (het)			*IFNA8* (het)/; *TLR4* (het)/; *IRF2BPL* (het)			*UNC13D* (het)
P27	*UNG* (comp het)	*KMT2A* (het)			*TNFRSF11A* (het)		
P28	*DNMT3B* (hom)				*NLRP1* (comp het)	*NLRP12* (comp het)	*CFH* (het)/ *ELANE* (het)/; *SEMA3E* (het)

(Continued)

TABLE II. *(Continued)*

Patient ID	Main potential genetic cause of IEI	Potential modifiers in antiviral immunity-related pathways					
		Lymphocyte development/ epigenetic	DNA repair gene defect	IFN pathway genes	IL-1 activation pathway genes	NF-κB pathway genes	Other related genes*
P29	*BTK* (hem)		*CHD7* (het)	*STAT6* (het)/ *IFNLR1* (het)/ *IL28R* (het)		*NOD2* (het)	*IL4R* (het)
P30	*IL7R* (hom)	*KMT2D* (het)					
P31	*IL37* (hom)	*ERCC6L2* (het)			*PEPD* (het)/*PRKCD* (het)/*MVK* (het)		

Comp het, Compound heterozygous; *hem,* hemizygous; *het,* heterozygous; *hom,* homozygous.
*Known IEI genes associated with autoinflammatory disease, disease of immune dysregulation, and complement deficiencies.

TABLE III. Specific antibody response against spike (S1-S2) and receptor-binding domain (RBD) antigens in 29 IEI patients with severe/critical COVID-19

Patient ID	IEI	Days after onset of infection	S1-S2			RBD		
			IgM AU/mL (1:3200)	IgA AU/mL (1:1600)	IgG AU/mL (1:6400)	IgM AU/mL (1:1600)	IgA AU/mL (1:1600)	IgG AU/mL (1:1600)
Cutoff	—	—	2.5	0.5	0.03	8.4	0.08	14.8
P1	Hyper-IgM syndrome	21	38.31*	0	0	14.86*	0	3.84
P2	Immune dysregulation	7	0	0	0	0	0	0
P3	Immune dysregulation	9	109.47*	17.67*	84.58*	128.24*	18.12*	955.60*
P4	Innate immunodeficiency	5	5.18*	24.51*	1.09*	5.60	27.22*	20.46*
P5	CID	8	44.25*	23.18*	21.10*	109.35*	11.30*	120.40*
P6	CID	9	0	0	1.91*	0	0	19.76*
P7	Innate immunodeficiency	7	0	0	43.54*	0	0	246.61*
P8	Immune dysregulation	7	0	0	0	0	0	0
P9	Immune dysregulation	5	40.53*	4.54*	6.39*	37.83*	0	33.05*
P10	CID	8	30.39*	0	0	19.00*	0	19.76*
P11	CID	4	0	0	2.29*	0	0	0
P12	Innate immunodeficiency	9	0	0	0	0	0	0
P13	Autoinflammatory disorders	7	0	0	0	0	0	0
P14	CID	15	67.80*	28.86*	213.05*	66.55*	8.20*	0
P15	Immune dysregulation	10	61.91*	52.01*	171.67*	67.08*	87.54*	0
P16	Innate immunodeficiency	16	85.08*	40.10*	62.07*	41.37*	29.34*	359.96*
P17	Autoinflammatory disorders	13	42.65*	31.87*	99.23*	13.66*	19.75*	531.38*
P18	CID	11	102.05*	103.97*	79.31*	96.75*	33.59*	467.53*
P19	Innate immunodeficiency	14	0	0	0	0	0	0
P20	SCID	9	0	0	17.56*	0	0	22.56*
P21	Immune dysregulation	8	0.94	0	0	2.24	0	9.59
P22	Innate immunodeficiency	8	0	0	0	0	0	0
P23	Immune dysregulation	7	38.93*	0	0	40.29*	0	22.56*
P24	Autoinflammatory disorders	8	0	0	0	1.10	0	23.26*
P25	CID	8	37.34*	12.58*	4.02*	14.56*	1.19*	29.55*
P26	Innate immunodeficiency	10	0	0	0	0	0	0
P27	Innate immunodeficiency	9	2.75*	0	0	0	0	5.59
P28	SCID/CID	21	0	0	0	0	0	6.93
P29	Agammaglobulinemia	27	0	0	0	0	0	0

Cutoff determined on the basis of negative controls collected before pandemic time and the cohort of PCR-confirmed COVID-19 patients with no known IEI.[39] *SCID,* Severe CID.
*Positive sample.

were negative in all tested patients. To investigate whether autoantibody production against IFN-I could explain some cases of severe/critical COVID-19 in this cohort, we measured plasma levels of autoantibodies against multiple interferons as well as other cytokines in 29 patients. We identified 2 patients (P5, P23; 6.8%) with raised plasma levels of autoantibodies against IFN-I, including IFNA1, IFNA2, IFNA4, IFNA5, IFN6, IFNA8, IFNA10, IFNA17, and IFNA21 (see Fig E4 in the Online Repository available at www.jacionline.org). Plasma from these 2 patients also showed neutralizing activity for anti-IFNA2 and anti-IFNW. P5 was diagnosed before COVID-19 with CID (normal T-cell counts but a diminished lymphocyte transformation test and a history of severe influenza infection) and P23 with immune dysregulation associated with hemophagocytic lymphohistiocytosis (the result of cytomegalovirus and with a history of varicella zoster pneumonia). P5 had a heterozygous mutation in *NFKB1* (in addition to mutations in several potential modifier genes including *IFNA8* and *IL17RD*), and P23 had a

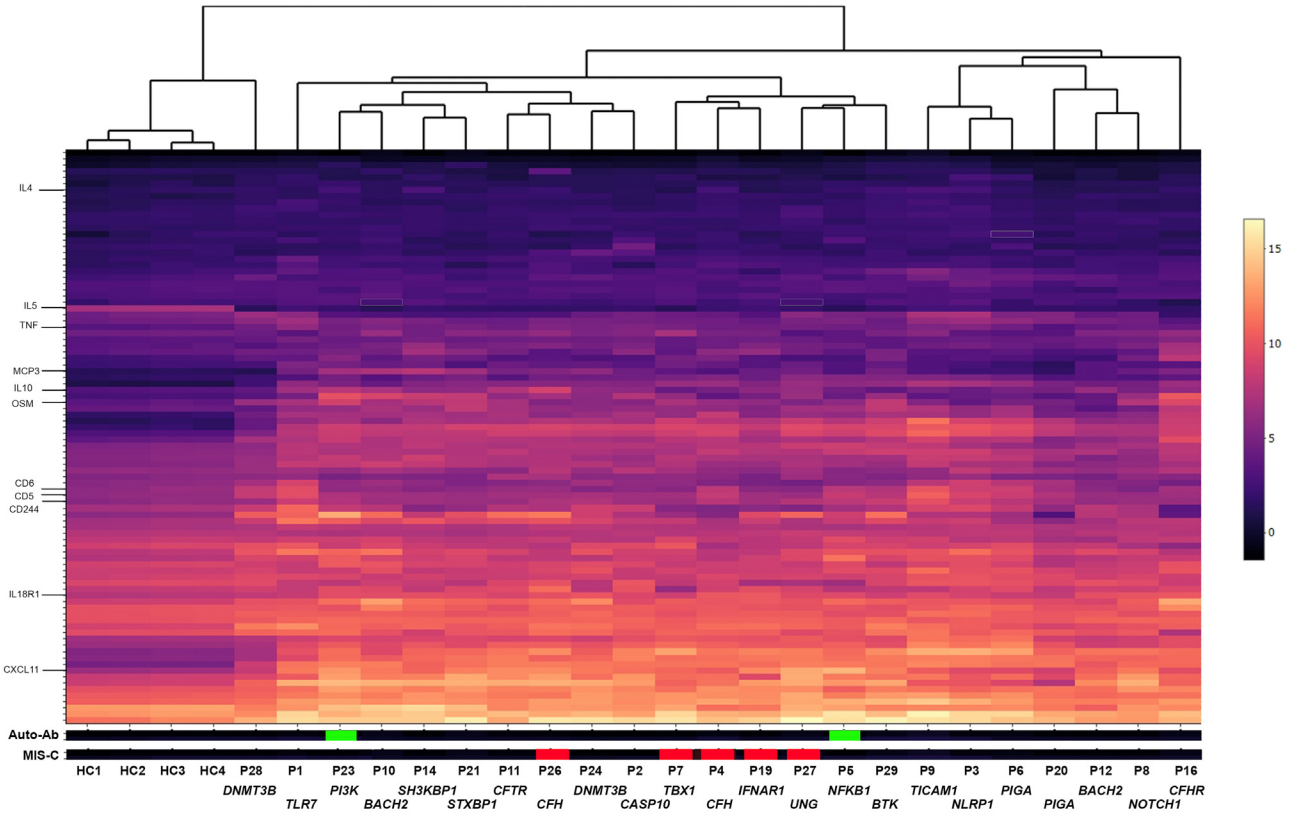

FIG 3. Heat map analysis of plasma level of the inflammatory proteins in IEI patients with severe or critical COVID-19. Each *column* represents a patient, and each *row* indicates a given protein measured. *Green bars* indicate patients with autoantibodies against IFN-I *(Auto-Ab); red bars* indicate IEI patients who presented with MIS-C. The color legend is presented as normalized protein expression (NPX) values, Olink Proteomics' arbitrary unit on a $\log_2$ scale. Details of measurement of each protein are shown in Table E4 and differentially expressed markers are depicted in Fig E5.

heterozygous mutation in *PIK3CD* (in addition to several potential modifier genes including variants of *IL34* and *IL7R*). Of note, the *NFKB1* variant was located in the ankyrin repeat domain in the C-terminal half of p105 precursor,[55] and recent biochemical analyses suggested that none of the variants in the ankyrin repeat domain was loss of function or hypomorphic.[56,57] It is possible and remains to be proven that this missense variant is a gain of function by affecting the inhibitory regulation of the canonical NF-κB signaling.

None of the patients with MIS-C presentation was positive for autoantibodies against IFNs; however, a large deletion in the *IFNAR1* gene was identified in 1 critically ill patient with concomitant COVID-19 pneumonia and typical Kawasaki disease (KD) who died of complications of the SARS-CoV-2 infection (P19, reported[35]). Interestingly, 2 other MIS-C patients were diagnosed with innate IEI before COVID-19 where *CFH* mutations were identified in both cases (P4 concomitant with COVID-19 pneumonia, and P26 critical condition leading to death), and both presented with vasculitis, thrombocytopenia, proteinuria, and reduced serum levels of complement component C3. MIS-C patients P7 and P27 had mutations in *TBX1* (heterozygous) and *UNG* (compound heterozygous), respectively.

To further understand the effect of the identified genetic defects on a system level, we monitored plasma proteins using the Olink inflammation panel. Notably, IEI patients with severe/critical COVID-19 had a significantly higher level of 22 inflammatory markers related to intense innate immune response and higher adaptive cytotoxic activity, including CD8A, CDCP1, CD244, IL-6, CXCL1, IL-18, TGFα, TNFSF14, IL-15RA, IL-18R1, CD274, HGF, IL-10, CD5, CCL3, CXCL10, EIF4EBP1, CD40, IL-33, CASP8, CCL20, and ADA compared to age-matched healthy controls (Fig 3; and see, in the Online Repository available at www.jacionline.org, Fig E5, Table E3, and Table E4). Notably, IEI patients with an MIS-C presentation clustered closely together (higher levels of CD6, CD244, CD5, IL-18R1, and CXCL11 and lower levels of IL-5, MCP3, IL-4, OSM, IL-10, and TNF), but the 2 patients with autoantibodies against IFN-I did not present a similar cytokine profile (Fig 3). The pattern of inflammatory markers in critically ill IEI patients was more similar to the observed markers in non-IEI patients with severe COVID-19 but distinct from non-IEI patients with mild infection or MIS-C (Fig 3, and, in the Online Repository, Fig E6, Table E3, and Table E4).

DISCUSSION

This study included children with preexisting IEI conditions, mainly with a clinical diagnosis of CID, immune dysregulation, or innate immunodeficiencies, who later developed severe or critical COVID-19. Detailed genetic and immunologic

evaluations of these young IEI patients suggest that deleterious genetic variants affecting lymphocyte development, the inflammasome pathway, and the IFN system as well as autoantibodies against IFN-I seem to contribute to the severity of the disease in these patients. Recent meta-analyses of 46 genome-wide association studies from 49,562 cases and 2 million controls indicated that in the normal population, the *ABO, PPP1R15A,* and *SLC6A20* loci impact susceptibility to infection, whereas genetic variants in the immune-related/IFN pathways including *TYK2, CXCR6, IFNAR2,* and *OAS* loci imply progression to severe/critical COVID-19.[58] Moreover, whole-genome sequencing in 7,491 critically ill patients compared to 48,400 controls highlighted the importance of immune-related genes variants in IFN signaling (*IFNA10, IFNAR2, TYK2, IL10RB,* and *PLSCR1*), leucocyte differentiation (*BCL11A*), and myeloid cell adhesion (*SELE, ICAM5,* and *CD209*) in the predisposition to critical COVID-19.[59] Our study reinforces the notion that genetic defects in the IFN-I pathway can lead to hypoxemic COVID-19 pneumonia, and furthermore suggests that additional pathways, such as lymphocyte development, the inflammasome, and complement pathways, may also be associated with a severe/critical form of COVID-19.

Autoantibodies against IFN-I were detected in 2 (6.8%) of the investigated patients with IEI. It has been shown that monogenic inborn errors of IFN-I immunity underlie ~5% of patients with severe and critical COVID-19, as well as other selected severe viral infections or adverse effects of live-attenuated vaccines.[60-67] Furthermore, autoantibodies neutralizing IFN-I are present in at least 15% of the severe cases in the general population.[6,22] These findings show that IFN-I is essential for protective immunity against SARS-CoV-2. The proportion of IFN-I autoantibody positivity of the investigated IEI patients was similar to that of adult non-IEI severe COVID-19 patients. Children with COVID-19 present higher mucosal levels of IFN-I than adults, potentially leading to a less severe phenotype and a less severe outcome.[68] Hitherto, however, to our knowledge, there has been no study on immunocompetent children with COVID-19 where IFN-I autoantibodies have been evaluated. However, a disease-specific study of 22 patients with autoimmune polyendocrine syndrome type 1 (from the IUIS immune dysregulation category) with preexisting autoantibodies to IFN-I showed that these patients are more prone to hospitalization after SARS-CoV-2 infection, and 18% died.[69]

Tight regulation of B-cell receptor signaling is essential for central and peripheral tolerance, and consequently the elimination of autoreactive B cells in the periphery, thus preventing the production of IFN autoantibodies. Moreover, clearance of apoptotic cells and immune complexes might be dysfunctional during chronic infection and recurrent inflammation, which may predispose to self-tolerance breakage. Both mechanisms have been shown to be defective in IEI patients with genetic mutations in the PI3K and NF-κB pathways, and therefore the majority of them present with autoimmunity.[70,71] Further investigations will be required to address whether the *PIK3CD* and *NFKB1* mutations also underlie the production of autoantibodies against IFN-I in the 2 autoantibody-positive patients described here.

MIS-C was observed both in isolated and combined forms in this pediatric IEI cohort. We have previously shown that MIS-C concomitant with critical pneumonia can be due to IFNAR1 deficiency,[35] and here we presented 1 additional case (with a *CFH* mutation) in a combined form (MIS-C and pneumonia) as well as 3 patients with an isolated form of MIS-C (without pneumonia) associated with other immunodeficiency (with *CFH, TBX1,* and *UNG* mutations). Among these newly identified genes, *CFH* was observed in 2 of our MIS-C cases with or without concomitant pneumonia. There is accumulating evidence showing that risk factor variants in complement-related genes, mainly *CFH,* are associated with severe COVID-19 and a decreased deposition of *CFH* in COVID-19–infected lung tissue.[72-74] We have, however, not observed an enrichment of *CFH* mutations in a cohort of MIS-C patients without preexisting IEI (data not shown). A previous investigation has shown that the inflammatory response in MIS-C differs from the cytokine storm of severe acute COVID-19 but shares several features with KD (elevated IL-6, CXCL10). MIS-C also differs from KD by showing lower level of IL-17A and immunosuppressive mediators like ADA, SCF, and TWEAK (negative regulator of IFN-γ and T_H1-type immune response).[47] However, our findings showed that MIS-C patients with an underlying IEI have a higher plasma level of chemokine receptors with overrepresentation of IL-18 signaling markers and lower levels of markers in the IL-10 signaling pathway, similar to severe COVID-19 patients, but clustered separately from MIS-C with no prior IEI condition and the mild COVID-19 cases (Fig E6).[47,48]

Recent population-based and single case studies have highlighted that certain immunocompromised individuals are at risk for prolonged and severe SARS-CoV-2 infection and poor clinical outcomes.[75] Our previous observation on the early phase of the pandemic on IEI-infected patients suggested a 42.1% mortality, whereas the current study focusing on severe/critically infected patients showed a slightly lower death rate (35.4%), potentially as a result of better clinical management. Of note, the epidemiological interpretation of these findings should be considered in light of the total number of IEI-infected patients (as many patients might be infected without overt COVID-19 signs).

We have further reviewed the available literature, and approximately 1210 IEI patients have been reported with COVID-19 worldwide (see Fig E7 and Table E5 in the Online Repository at www.jacionline.org). Predominantly antibody-deficient patients (58.9%, mainly common variable immunodeficiency) constitute the majority. Severe presentation of COVID-19 was observed in 21.5% of the reported IEI patients and was seen in a relatively higher proportion of patients with innate immune deficiency (48.2%) and IEI phenocopies (62.5%) (Fig 4). Furthermore, COVID-19–related mortality in these IEI patients was 8.3%, indicating a 4-fold higher mortality rate compared to the global case fatality of 2.0% in the general population. About 31.4% of the reported IEI patients with COVID-19 are children (n = 381) who mainly had *BTK* or IgG subclass deficiency. Severe presentation of COVID-19 was observed in 23.6% of pediatric IEI patients, with an overall fatality rate of 8.7%, which is about 870-fold higher than in children in the general population (~0.01%).[52] In our study, where only severe or critically ill IEI children were included, the fatality rate is, as expected, even higher (35.4%).

A relatively higher mortality was observed in all IUIS groups, especially in patients with IEI phenocopies (31.2%), nonsyndromic CID (15.7%), and syndromic CID (11.7%) compared to the normal population, except for complement deficiency (Fig 4). Male IEI patients with COVID-19 were predominant (59.3%); however, the male:female ratio was very high in COVID-19 patients with syndromic CID (4.4 vs 1.3, which is the global

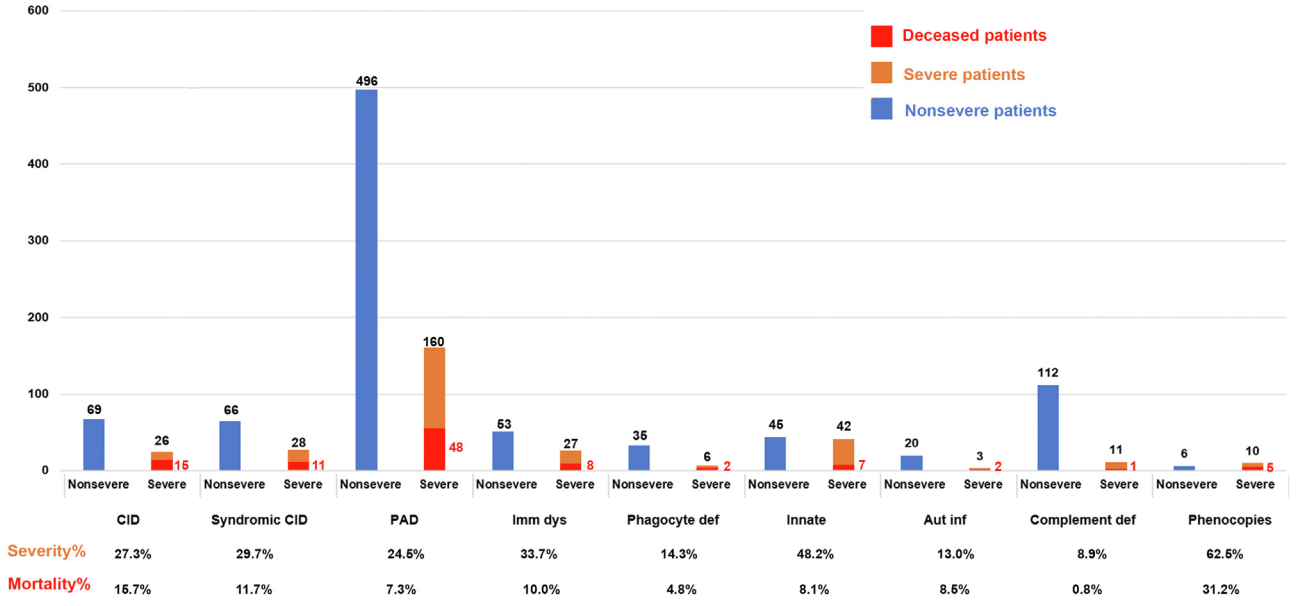

FIG 4. Systematic review of the literature on the frequency of severe and critical forms of COVID-19 in different entities of IEI patients based on IUIS classification. IEI phenocopies group refers to a group of patients with Good syndrome and somatic mutation in *TNFRSF6*. Details are shown in Table E5.

male:female ratio of this IEI entity).[76] Considering the sex ratio of the reported IEI patients, COVID-19–related mortality was slightly higher in male patients (64.5% of deceased patients). IEI male patients also died at a younger age compared to female patients (27.4 vs 50.8 years). There was no age difference between COVID-19 IEI patients compared to global IEI patients.[76] However, patients with phagocytic defects (median age, 9.2 years), diseases of immune dysregulation (median age, 9.4 years), autoinflammatory disorders (median age, 10 years), and nonsyndromic CID (median age, 10.2 years) showed a higher COVID-19–related mortality at younger ages compared to other IEI entities. A stratified analysis of pediatric IEI patients showed that even though PAD and innate immunodeficient patients have a higher frequency among severely ill patients, mortality is more often observed in CIDs and patients with immune dysregulation (62% and 14% of the total childhood mortality in the IEI cohort, respectively; see Fig E8 in the Online Repository available at www.jacionline.org).

The underlying molecular defect was identified only in 43.5% (1.4% chromosomal defect, 42.1% monogenic diseases) of the IEI patients with COVID-19 reported to date (Table E5). Mutations in *BTK* (n = 96 patients), *AIRE* (n = 30 patients), and *TLR7* (n = 28 patients) were the most frequently reported genetic defects in the SARS-CoV-2–infected patients. Severe and critical COVID-19 illness in IEI patients were reported frequently in patients with monogenic defects of *TLR7* and *NFKB2* (see Fig E9 in the Online Repository available at www.jacionline.org). The mortality rate was potentially high in patients with *XIAP* (2/3 patients), *IL1RN* (1/1 patient), *RAB27A* (1/1 patient), *CFI* (1/1 patient), and *STK4* (1/1 patient) deficiencies, although this needs to be confirmed by evaluation of additional patients with these rare monogenic IEI. However, the majority of mild–asymptomatic IEI patients might not be reported or were not genetically evaluated, which is required to make a more accurate evaluation of the molecular defects underlying different types of COVID-19 presentation in IEI patients.

Because the majority of genes reported in COVID-19 IEI patients are associated with autosomal recessive diseases (~65%, Table E5), the high percentage of consanguineous marriages in our study cohort (48.3%) may have increased the genetic diagnostic yield. In general, this rate of consanguinity in our cohort is slightly lower than that in the Iranian IEI registry (60.1%) but significantly higher compared to the global rate of 6.1%.[76] Of note, consanguinity was associated with a slightly increased frequency of lung complications and mortality, indicating that these autosomal recessive IEI patients are more prone to have early onset morbidity and mortality compared to other X-linked or autosomal-dominant genetic defects. Although all identified variants in this study fulfilled ACMG criteria and the mutations from selected patients in this genetically diagnosed cohort have been functionally characterized, biochemical validation should be performed in the future for the remaining novel variants.

The COVID-19 pandemic has provided the possibility to evaluate the immunopathogenesis of a severe infection caused by a single virus via a monogenic approach. Our study on young IEI patients with severe/critical COVID-19 can further help identify immunologic and genetic determinants of the populations at risk, and to develop optimal treatment and prevention strategies. Although the IEI community is aware of the health risks posed by this pandemic crisis and has tried to minimize their risk to community exposure, accumulated reports from us and others highlight the importance of genetic evaluation and continuous medical care for vulnerable IEI patients.[77] Besides standard-of-care treatment, early treatment with polyclonal or monoclonal anti–SARS-CoV-2 antibodies,[10,78,79] treatment with antiviral medications, vaccination prioritization, monitoring specific neutralizing antibody titers, the presence of autoantibodies against IFN-I, and cellular responses, as well as calibration of therapy according to the underlying genetic defect, potentially including interferon and anti-inflammatory drugs, might improve COVID-19 management, resulting in a lower mortality in IEI patients. Because this study was limited only to severe cases with

wild-type virus and without vaccination, further studies are needed to evaluate the impact of different variants of concerns and different types of vaccines on this specific group of patients. Moreover, the systematic review performed on published IEI patients has a potential bias, as some reports may still be missing as a result of the search strategy and keywords selected. However, our overall findings emphasize the need for a paradigm change about SARS-CoV-2–infected children, as severity and mortality are extremely high in pediatric patients with a history of IEI. Considering the increased hospitalization rates among unvaccinated infants and children due to the new SARS-CoV-2 variant circulation (eg, Omicron reached the current highest level of the pandemic), basic immunologic investigation and genetic evaluation are required in case the diagnosis of IEI is delayed or not established in children with severe forms of COVID-19 or MIS-C.

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Key messages

- **The IFN signaling, T- and B-cell function, the inflammasome, and the complement system were frequently affected either by gene defects or autoantibodies in a highly consanguineous pediatric IEI cohort.**
- **Selected IEI children can develop MIS-C, and these patients have distinct inflammatory profiles compared to other severe/critical IEI patients without MIS-C.**
- **Children with preexisting IEI may have more severe disease and higher mortality when infected with SARS-CoV-2.**

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