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# Coronavirus disease 2019 in patients with inborn errors of immunity: An international study



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**Background:** There is uncertainty about the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in individuals with rare inborn errors of immunity (IEI), a population at risk of developing severe coronavirus disease 2019. This is relevant not only for these patients but also for the general population, because studies of IEIs can unveil key requirements for host defense.

**Objective:** We sought to describe the presentation, manifestations, and outcome of SARS-CoV-2 infection in IEI to inform physicians and enhance understanding of host defense against SARS-CoV-2.

**Methods:** An invitation to participate in a retrospective study was distributed globally to scientific, medical, and patient societies involved in the care and advocacy for patients with IEI.

**Results:** We gathered information on 94 patients with IEI with SARS-CoV-2 infection. Their median age was 25 to 34 years. Fifty-three patients (56%) suffered from primary antibody deficiency, 9 (9.6%) had immune dysregulation syndrome, 6 (6.4%) a phagocyte defect, 7 (7.4%) an autoinflammatory disorder, 14 (15%) a combined immunodeficiency, 3 (3%) an innate immune defect, and 2 (2%) bone marrow failure. Ten were asymptomatic, 25 were treated as outpatients, 28 required admission without intensive care or ventilation, 13 required noninvasive ventilation or oxygen administration, 18 were admitted to intensive care units, 12 required invasive ventilation, and 3 required extracorporeal membrane oxygenation. Nine patients (7 adults and 2 children) died.

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**Conclusions:** This study demonstrates that (1) more than 30% of patients with IEI had mild coronavirus disease 2019 (COVID-19) and (2) risk factors predisposing to severe disease/mortality in the general population also seemed to affect patients with IEI, including more younger patients. Further studies will identify pathways that are associated with increased risk of severe disease and are nonredundant or redundant for protection against SARS-CoV-2. (J Allergy Clin Immunol 2021;147:520-31.)

**Key words:** SARS-CoV-2, COVID-19, primary immunodeficiencies, inborn errors of immunity, hypogammaglobulinemia, immune dysregulation

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus, emerged in the Hubei province of China as a novel human pathogen. SARS-CoV-2 causes an infectious disease (coronavirus disease 2019 [COVID-19]) characterized by pneumonia and acute respiratory failure.<sup>1-4</sup> SARS-CoV-2 infects human cells by binding to the angiotensin-converting enzyme 2, which is expressed predominantly by lung and intestinal epithelial cells, alveolar cells, and vascular endothelial cells. SARS-CoV-2 spreads within the human population mainly via droplet transmission and has infected more than 40 million individuals, causing more than 1.1 million deaths. There is a broad clinical spectrum including asymptomatic infection, mild infection (fever, fatigue, diarrhea, vomiting, myalgia, dry cough, dyspnea, and pneumonia), respiratory failure, myocarditis, thromboembolism, and finally fatal multiorgan failure.<sup>5,6</sup> The pathophysiology of COVID-19 results from direct cytopathic effects of SARS-CoV-2 on respiratory epithelia, endothelia, and other organ-specific cell types, and subsequent induction of a proinflammatory cytokine storm and dysregulated adaptive immunity causing severe tissue damage.<sup>7</sup>

Current epidemiology studies indicate that the case-fatality rate of SARS-CoV-2 infection ranges from 1% to 20%, while

#### Abbreviations used

AGS:	Aicardi-Goutieres syndrome
AIHA:	Autoimmune hemolytic anemia
ALPS:	Autoimmune lymphoproliferative syndrome
AR:	Autosomal-recessive
CGD:	Chronic granulomatous disease
CID:	Combined immunodeficiency
COVID-19:	Coronavirus disease 2019
CVID:	Common variable immune deficiency
HLH:	Hemophagocytic lymphohistiocytosis
HSCT:	Hematopoietic stem cell transplantation
ICU:	Intensive care unit
IEI:	Inborn errors of immunity
P:	Patient
PID:	Primary immunodeficiency
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2
X-CGD:	X-linked chronic granulomatous disease
X-SCID:	X-linked severe combined immunodeficiency

the infection fatality rate is 0.2% to 1.3%.<sup>8,9</sup> Despite this variability, the lethality of SARS-CoV-2 infection consistently and dramatically increases with each decade of life beyond age 50 years<sup>10</sup> (Table 1). Furthermore, pre-existing comorbidities (chronic lung/heart disease, obesity, diabetes, hypertension) have been reported to contribute to a more severe course of COVID-19.<sup>11,12</sup> Importantly, the occurrence of a multisystemic hyperinflammatory syndrome in children (MIS-C) has challenged the perception that SARS-CoV-2 infection is mild in young individuals.<sup>13,14</sup> In most countries, more males than females have presented with symptomatic SARS-CoV-2 infection, indicating that sex can influence disease course and/or outcome.<sup>10</sup>

Another contributor to interindividual susceptibility to severe COVID-19 and outcome postinfection is genetic heterogeneity.<sup>15</sup> This reflects the discoveries of patients with inborn errors of immunity (IEI) who exhibit increased susceptibility to pathogen

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**TABLE I.** Age distribution and lethality of SARS-CoV-2 infection in patients with IEI

Patients with inborn errors of immunity					General population					
Age group (y) (94 cases)	M:F	COVID-19 cases per age group in our cohort, N (%)	Deaths in our cohort, N (%)	ICU admission, N (%)	Age groups general population (y)	COVID-19 cases per age group (general population), %		Deaths (general population), %		ICU admission (general population), %
0-2	6:1	7 (7.4)	1 of 7 (14)	3 of 7 (43)	0-9	1.5*	4.2†	0.1*	0.1‡	0.7*
3-12	12:5	17 (18)	0 of 17	2 of 17 (12)						
13-18	4:4	8 (8.5)	1 of 8 (10)	4 of 8 (50)	10-19	3.7	7.8	0.1	0.2	0.4
19-24	4:0	4 (4.2)	0 of 4	0 of 4	20-29	13.8	20.0	0.1	0.2	0.5
25-34	10:3	13 (13.8)	0 of 13	0 of 13	30-39	16.3	17.8	0.4	0.2	0.9
35-44	9:6	15 (16)	2 of 15 (13)	3 of 15 (20)	40-49	16.6	14.4	1.0	0.3	1.5
45-54	8:1	9 (9.5)	0 of 9	1 of 9 (11)	50-59	17.9	12.7	2.4	0.8	2.5
55-64	5:5	10 (10.6)	2 of 10 (20)	3 of 10 (30)	60-69	13.6	7.6	6.7	2.7	4.1
65-74	0:5	5 (5.3)	0	0	70-79	8.0	5.3	16.6	8.0	5.6
>75	2:3	5 (5.3)	3 (60)	2 (40)	>80	8.7	10.0	28.7	16.0	3.6
All patients	65:35 (1.8:1)	NA	10 (10)	20 (20)	All			5.4 (1-20)		2.3

F, Female; M, male; N, absolute number.

Data for the general population are all taken from Stokes et al.<sup>10</sup>

\*Data from the United States, n = 1,320,488 cases.<sup>10</sup>

†Data from the United Kingdom, n = 73,359 cases (<https://www.gov.uk/government/publications/demographic-data-for-coronavirus-testing-england-28-may-to-26-august/demographic-data-for-coronavirus-covid-19-testing-england-28-may-to-26-august>).

‡<https://ourworldindata.org/covid-deaths>; average of data from Spain, Italy, China, and South Korea.

infection.<sup>16,17</sup> Although more than 430 monogenic IEIs have been described,<sup>16-18</sup> the consequences of SARS-CoV-2 infection have been reported for only a few individuals with these conditions.<sup>19-22</sup>

Thus, the aim of this multicenter, retrospective international study was to assess the impact of SARS-CoV-2 infection on patients with IEIs, thereby providing the first comprehensive description on the susceptibility of an at-risk population of patients to SARS-CoV-2 infection, as well as their COVID-19 clinical course, severity, complications, and outcomes. This extensive global data set represents an important reference for clinicians treating and managing patients with IEIs in the context of the COVID-19 pandemic.

## METHODS

A retrospective study was undertaken by a web-based survey, approved by the University Hospitals Leuven Committee for Medical Ethics. The questionnaire inquired about demographic data, COVID-19 presentation, treatment, and outcomes in patients with IEIs (according to current diagnostic guidelines) and documented SARS-CoV-2 infection. No identifying information was required, while physicians were given the option of providing their contact details. The survey opened on March 16, 2020, and closed on June 30, 2020. An invitation to participate in the survey was shared with members of various societies (European Society for Immunodeficiencies, Clinical Immunology Society, Latin American Society for Immunodeficiencies, African Society for Immunodeficiencies, Asia Pacific Society for Immunodeficiencies, Australasian Society for Clinical Immunology & Allergy), as well as via the International Patient Organization for Primary Immunodeficiencies, the Jeffrey Modell Foundation, and the International Union of Immunological Societies Committee for Inborn Errors of Immunity, with the aid of social media alerts. Fisher exact test of independence and Bayesian analysis of contingency tables were used to calculate the statistical significance of the correlation between categorical variables.

## RESULTS

### Patients

A total of 94 patients with an underlying primary immunodeficiency (PID)/IEI and infected by SARS-CoV-2, as determined by serology (n = 8) or diagnostic PCR (n = 86), were reported (Tables I and II). Male to female ratio was 1.8 to 1. Thirty-two patients were younger than 18 years and 62 were adults (median age group, 25-34 years). Eleven patients have been reported previously.<sup>19-21,23</sup>

### Types and causes of IEI

The distribution of patients according to IEI groups is shown in Fig 1. Most patients had a pre-existing primary antibody deficiency (53 of 94 [56%]), including

- 6 with X-linked agammaglobulinemia due to *BTK* variants (patient [P] 18, P44, P50, P54, P57, and P58);
- 2 patients with heterozygous *NFKB1* (P53 and P60) or *NFKB2* (P10 and P13) variants;
- 1 patient with X-linked severe combined immunodeficiency (X-SCID) who underwent gene therapy 19 years earlier that corrected his T cells but not B cells, thereby remaining antibody deficient (P43);
- 2 cases of autosomal-recessive (AR) agammaglobulinemia (P11 and P64) (Fig 1 and Table II).

There were also 29 patients with common variable immune deficiency (CVID) and 2 patients with syndromic features (P1: cardiomyopathy and neutropenia; P41: ventricular septum defect and CD4<sup>+</sup> T-cell lymphopenia; Table II). Forty-six of 53 antibody-deficient patients received immunoglobulin substitution as standard therapy and 6 received immunosuppressive therapy.

Six patients had phagocyte defects: 4 with X-linked (variants in *CYBB* [P8, P88, and P92]) or recessive (biallelic variants in *NCF2*



[P89]) chronic granulomatous disease (CGD); 1 (P88) was treated with cyclosporin (Fig 1 and Table II). Fourteen patients had combined immunodeficiencies (CIDs), including 10 with syndromic features: Di George syndrome (P27); trisomy 21 (Down syndrome [P15, P17, and P26]),<sup>24,25</sup> Wiskott-Aldrich syndrome (P16: 3 months post-hematopoietic stem cell transplantation [HSCT]; P35: 5 months post-gene therapy), *ARPC1B* deficiency (P25), hyper-IgE syndrome due to heterozygous dominant negative variants in *STAT3* (P77 and P78), or biallelic variants in *PGM3* (P76). Other patients had pathogenic biallelic variants in *ZAP70* (P73) or *IFNGR2* (P38), or heterozygous gain-of-function variant in *STAT1* (P93). P7 had chronic mucocutaneous candidiasis and recurrent pyogenic sepsis, suggesting an underlying innate immune defect. Nine patients presented with an immune dysregulation syndrome: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (due to biallelic *AIRE* variants [P87]); *LRBA* deficiency (P86); *CTLA4* haploinsufficiency (P31 [post-HSCT, poor graft function] and P32); autoimmune lymphoproliferation due to pathogenic variants in *PRKCD* (biallelic; P84), or *XIAP* (P9, 4 months post-HSCT); autoimmune lymphoproliferative syndrome (ALPS)-like disease (P36 and P85); and prolidase deficiency due to biallelic pathogenic variants in *PEPD* (P30) (Fig 1 and Table II). The *LRBA*-deficient, *PRKCD*-deficient, X-linked inhibitor of apoptosis-deficient, ALPS-like, *PEPD*-deficient and 1 of the *CTLA4*-deficient patients (P32) received immunosuppressive treatment (abatacept [n = 2], mycophenolate [n = 1], steroids [n = 3], sirolimus [n = 2], everolimus [n = 1]) (Table II).

Seven additional patients suffered from an autoinflammatory disease (Fig 1 and Table II):

- Aicardi-Goutieres syndrome (AGS) due to biallelic *RNA-SEH2B* variants (P81 and P82), treated with immunoglobulin substitution and JAK inhibitors, or homozygous *SAMHD1* pathogenic variants (P83);
- familial Mediterranean fever (*MEFV* variant [P28, P79, and P80]), treated with anakinra, canakinumab, and/or colchicine; and
- an autoinflammatory condition with lymphopenia and autoimmune hemolytic anemia (AIHA), treated with steroids (P29).

One patient suffered from bone marrow failure caused by biallelic *DNAJC21* mutations (P36), and 1 had pancytopenia due to a heterozygous *GATA2* variant (P94) (Fig 1 and Table II).

Before infection, all patients were stable on standard of care treatment; 2 were on angiotensin-converting enzyme inhibitor therapy. The most frequent presenting symptoms were fever (69%) and cough (47%), followed by upper respiratory tract symptoms (runny nose, sneezing: 19%) and shortness of breath/dyspnea (13%). Gastrointestinal symptoms (diarrhea, vomiting) and myalgia were reported in 14% and 16% of patients, respectively, while acute respiratory insufficiency was the presenting feature in 11% of patients. Other reported symptoms were fatigue, sore throat, anosmia/ageusia, collapse, pallor, and anemia.

### Clinical features of SARS-CoV-2<sup>+</sup> patients with IEI

Ten (11%) patients were asymptomatic (ALPS-like [P85], AGS [P81 and P82], *STAT1* gain-of-function [P93], Wiskott-Aldrich syndrome [P35], ARCGD [P89], XLA [P56], AR

agammaglobulinemia [P64], hypogammaglobulinemia [P40], and CID [P74]), including 4 who had pre-existing lung disease (Table II). In these cases, testing for SARS-CoV-2 was performed only to enable travel, elective treatment, or due to positivity of a symptomatic relative/close contact.

Twenty-four patients had mild disease and were treated as outpatients (Table II). Two were 3-12 years old, 1 was 19-24 years, 6 were 25-34 years, 5 were 35-44 years, 3 were 45-54 years, 2 were 55-64 years, 4 were 65-74 years, and 1 was older than 75 years. These patients included

- 14 with predominantly antibody deficiency (11 with CVID, of whom 7 had  $\geq 1$  comorbidity);
- 1 patient with X-SCID with persistent defective B-cell function after gene therapy;
- 1 with activated PI3 kinase syndrome (P51, *PIK3R1* mutation);
- 1 with CID with multiple autoimmune features (P75);
- 3 with hyper-IgE syndrome due to *PGM3* deficiency (P76), or *STAT3* loss of function (P77 and P78) including 1 with chronic lung disease; and
- 2 with *MEFV* mutations (P79 and P80), 1 with AGS (P83, *SAMHD1* mutation), 1 with CGD due to *CYBB* mutation (P92), and 1 with an unspecified phagocyte defect (P90).

Fifty-nine patients (63%) required hospitalization. Clinical progression of 29 of these 59 patients evolved into respiratory insufficiency (49% of hospitalized, 31% of all patients). Thirteen patients required noninvasive ventilation/oxygen administration, and 15 (11 males, 4 females; 16% of all patients) were admitted to intensive care units (ICUs) for invasive ventilation, including extracorporeal membrane oxygenation (3 male patients, 2 succumbed, see below). In addition, individual patients were admitted to ICU for severe AIHA (P36), hypotension (P94), or MIS-C and miliary *Mycobacterium avium* infection (P38; *IFNGR2*) but no respiratory complications. Among female patients admitted to ICU for respiratory insufficiency, 2 had CVID and were aged 55-64 years (P3 and P4), 1 was older than 75 years (hypogammaglobulinemia; P5), and one was younger than 2 years with trisomy 21 and chronic invasive ventilation via tracheostomy in the context of congenital heart disease (P17). In contrast, the age distribution of the 11 affected males admitted to ICU was broader than for females, and the general population (Tables I and II):

- 1 aged 0-2 years (P8 [X-linked chronic granulomatous disease, X-CGD]);
- 2 aged 3-12 years (P15 [trisomy 21] and P16 [Wiskott-Aldrich syndrome]);
- 2 aged 13-18 years (P13 [*NFKB2*] and P9 [*XIAP*]);
- 3 aged 35-44 years (P10 [*NFKB2*], P17 [agammaglobulinemia], and P1 [syndromic primary antibody deficiency]);
- P14, aged 45-54 years, and P12, aged 55-64 years, both with CVID; and
- 1 patient 75 years or older (P6 [IgG<sub>2</sub>/IgA deficiency]).

The three patients with trisomy 21 experienced acute respiratory insufficiency, requiring invasive (P15 and P17) or noninvasive (P26) ventilation. P15 and P17 also had a pre-existing heart condition; P17 required a tracheostomy and chronic ventilation. Overall, 73% (11 of 15) of the patients needing invasive ventilation had pre-existing comorbidities (Fig 1 and Table II).

TABLE II. Summary of patients' characteristics

Pt. no.	Outcome	PID	Age group (y)	Sex	Comorbidities	Usual therapy	Manifestations				
							Fever	Cough	URS	GI	Myalgia
1	Deceased	Ab def. Syndromic presentation	35-44	M	Neutropenia, dysmorphism, developmental delay, hypertrophic cardiomyopathy	Ig, G-CSF	X	X			Chest pain
2	Deceased	Ab def. CVID	35-44	F	Kidney tx, lymphoma and cervical cancer in remission	Ig, steroids					Hypotension, renal failure
3	Deceased	Ab def. CVID	55-64	F	Lung disease, heart disease, ITP	Ig, rituximab, metoprolol	X	X			Dyspnea, fatigue, hypotension, renal failure
4	Deceased	Ab def. CVID	55-64	F	Lung disease	Ig	X	X			
5	Deceased	Ab def. IgG deficiency	≥75	F	Lung disease, heart disease, kidney disease, hypertension, diabetes	Ig	X	X			Dyspnea, hypotension, renal failure
6	Deceased	Ab def. IgG <sub>2</sub> and IgA deficiency	≥75	M	Diabetes, AIHA	Ig	X				Hypotension, renal failure
7	Deceased	Ab def. CVID	≥75	F	Lymphoproliferative disease, GI disease, genital tract neoplasm	Ig					Acute confusional syndrome
8	Deceased	Phagocyte defects CGD ( <i>CYBB</i> )	0-2	M	—	—	X				<i>Burkholderia</i> sepsis
9	Deceased	Immune dysregulation disorder ( <i>XIAP</i> )	13-18	M	4 mo post-HSCT, severe gut GvHD	Antibiotics, antifungals, Ig, steroids, cyclosporine	X				Collapse
10	Resolved	Ab def. CVID ( <i>NFKB2</i> )	35-44	M	—	Ig, antibiotics, antivirals, mAb	X	X	X		
11	Resolved	Ab def. Agammaglobulinemia	35-44	M	Lung disease	Ig, steroids, antibiotics, GM-CSF	X	X		X	
12	Resolved	Ab def. CVID	55-64	M	Asthma	Ig, immunosuppressive	X	X		X	
13	Resolved	Ab def. CVID ( <i>NFKB2</i> )	13-18	M	Alopecia tot., psoriasis	—	X	X	X	X	Dyspnea
14	Resolved	Ab def. CVID	45-54	M	Lung disease	Ig, immunosuppressive	X	X			
15	Resolved	CID Trisomy 21	3-12	M	Lung disease, heart disease, pulmonary hypertension, mental disability	Antibiotics, Ig, antivirals, steroids	X	X		X	
16	Still in ICU	CID Wiskott-Aldrich syndrome	3-12	M	3 mo post-HSCT, GI disease	Antibiotics, Ig, steroids	X	X			CMV encephalitis, anosmia
17	Still in ICU	CID Trisomy 21	0-2	F	Heart defect, tracheostomy with chronic ventilation	Antibiotics, Ig					
18	Resolved	Ab def. XLA ( <i>BTK</i> )	3-12	M	Spherocytosis	Ig	X	X		X	Dyspnea, chest pain
19	Resolved	Ab def. CVID	25-34	F	—	Ig	X	X			Anosmia
20	Resolved	Ab def. CVID	25-34	M	—	Ig	X	X		X	Fatigue
21	Resolved	Ab def. CVID	45-54	M	Lung disease	Ig, antibiotics	X	X			
22	Resolved	Ab def. CVID	45-54	M	Lung disease	Ig, antibiotics	X		X	X	
23	Resolved	Ab def. Hypogammaglobulinemia	45-54	F	Diabetes, heart disease, hypertension, neuropathy, mitochondrial myopathy	Ig, antibiotics, antifungals, ACE inhibitor, atorvastatin, bisoprolol, eplerenone, metformin, insulin	X	X			Neuropathy
24	Resolved	Ab def. CVID	45-54	M	Large granular lymphocyte leukemia	Ig	X	X			
25	Resolved	CID <i>ARPC1B</i>	0-2	M	Eczema, cow milk protein allergy	Antibiotics, Ig	X				Collapse
26	Resolved	CID Trisomy 21	3-12	M	—	—	X	X			Coinfection with <i>Mycoplasma pneumoniae</i>
27	Resolved	CID DiGeorge syndrome	0-2	M	Lung disease, tracheostomy with chronic ventilation	Antibiotics, Ig	X				
28	Resolved	Autoinflammatory disorder ( <i>MEFV</i> )	55-64	M	Lung disease	—	X	X	X	X	Dyspnea
29	Resolved	CID with immune dysregulation and autoinflammation	35-44	M	Hyporegenerative anemia, AIHA, intermittent renal insufficiency	Status post rituximab, steroids	X	X			Dyspnea Coinfection with CoV229E
30	Resolved	Immune dysregulation disorder ( <i>PEPD</i> )	25-34	M	Kidney disease, mental disability	Steroids, antibiotics, antivirals, antifungals, mAb	X	X			
31	Resolved	Immune dysregulation disorder ( <i>CTLA4</i> )	13-18	F	Lung disease, post-HSCT with poor graft function	Ig, antibiotics, antivirals, antifungals,					Dyspnea
32	Resolved	Immune dysregulation disorder ( <i>CTLA4</i> )	25-34		Lung disease, GI disease, chronic JCV cystitis	Steroids, Ig, everolimus, abatacept	X				Anosmia, ageusia
33	Resolved	Ab def. CVID	35-44	M	Lung disease	Antibiotics, antivirals	X	X		X	Dyspnea, fatigue
34	Resolved	Ab def. Isolated IgG subclass def.	55-64	F	Lung disease	Antibiotics, Ig, omalizumab					Dyspnea
35	Resolved	CID Wiskott-Aldrich syndrome	0-2	M	5 mo after gene therapy	Ig, prophylactic antivirals, pentamidine, thrombopoietin agonist					Asymptomatic
36	Resolved	Immune dysregulation disorder ALPS-like	13-18	M	Immune thrombocytopenia	Mycophenolate, eltrombopag	X		X		Anemia, jaundice
37	Resolved	CMC and recurrent sepsis	0-2	M	—	Ig	X	X	X		
38	Resolved	MSMD IFNGR2 deficiency	0-2	M	—	—	X	X			Miliary <i>Mycobacterium avium</i> coinfection, leukocytosis
39	Resolved	Bone marrow failure ( <i>DNAJC21</i> )	3-12	M	Exocrine pancreas insufficiency, failure to thrive, cytopenias, bone anomalies, mental disability	Antibiotics, red blood cell transfusions	X				Increased anemia and thrombocytopenia
40	Resolved	Ab def. Hypogammaglobulinemia	3-12	M	Uveitis	Ig					Asymptomatic

Respiratory insufficiency	Invasive ventilation	Severity	Complications	Therapy	Country	Seroconversion	Estimated duration of SARS-CoV-2 PCR positivity	Duration of infection/symptoms
X	ECMO	ICU admission	Pneumothorax, pulmonary hypertension, heart failure	Antibiotics, steroids, Ig	France			
		Hospital admission	Renal failure	Antibiotics, chloroquine, enoxaparin, conv. plasma	USA			
X	X	ICU admission	Renal failure	Antibiotics, chloroquine, enoxaparin	USA			
X	X	ICU admission	Sepsis	Antibiotics, steroids, tocilizumab, lopinavir, ritonavir	Italy	No	17 d (until death)	17 d (until death)
X	X	ICU admission	Renal failure	Antibiotics, chloroquine, enoxaparin	USA			
X	X	ICU admission	Renal failure	Antibiotics, chloroquine, enoxaparin	USA			
		Hospital admission	<i>E faecium</i> sepsis, renal failure	Antibiotics, chloroquine	Spain			
X	ECMO	ICU admission	HLH	Antibiotics, steroids	France			
X	X	ICU admission	Sepsis, HLH	Antibiotics, Ig	Chile			
X	X	ICU admission	Bacterial pneumonia	Antibiotics, Ig, hydroxychloroquine, remdesivir, lopinavir, ritonavir, tocilizumab	Italy			
X	ECMO	ICU admission	HLH	Antibiotics, steroids, chloroquine, GM-CSF, conv. plasma	Belgium		60-75 d	50 d
X	X	ICU admission	Sepsis (Candida)	Antibiotics, chloroquine, remdesivir, lopinavir, ritonavir, mAb	Italy	No	4 wk	
X	X	ICU admission	Sepsis HLH	Antibiotics, steroids, tocilizumab, remdesivir, conv. plasma	USA	Yes	8 d	
X	X	ICU admission	—	Steroids, chloroquine, tocilizumab remdesivir, lopinavir, ritonavir	Italy	No	9 d	
X	X	ICU admission	HLH	Antibiotics, steroids, Ig, remdesivir	Germany			
X	X	ICU admission	Bacterial pneumonia	Steroids, Ig	Mexico			
X	X	ICU admission	—	—	Chile			
X		Admission with O <sub>2</sub> /NIV	Bacterial pneumonia	Antibiotics, remdesivir, enoxaparin, conv. plasma	USA			
X		Admission with O <sub>2</sub> /NIV	—	Steroids, chloroquine, tocilizumab, lopinavir, ritonavir	Italy	No	9-50 d	
X		Admission with O <sub>2</sub> /NIV	—	Antibiotics, steroids	France	No		
X		Admission with O <sub>2</sub> /NIV	—	Antibiotics, Ig	France			
X		Admission with O <sub>2</sub> /NIV	—	Antibiotics	France	Yes (IgM)		2 mo
X		Admission with O <sub>2</sub> /NIV	—	Antibiotics	UK		15 d	18 d
X		Admission with O <sub>2</sub> /NIV	—	Antibiotics, chloroquine	Spain	Yes	30 d	17 d
X		Admission with O <sub>2</sub> /NIV	—	Antibiotics	Mexico			
X		Admission with O <sub>2</sub> /NIV	Neutropenia	Antibiotics	Belgium			
X		Admission with O <sub>2</sub> /NIV	—	Ig	Chile			
X		Admission with O <sub>2</sub> /NIV	—	Steroids, lopinavir, ritonavir	France			
		Hospital admission	Anemia, neutropenia	Chloroquine, lopinavir, ritonavir, tocilizumab	Germany	Yes	42 d	13 d
X		Admission with O <sub>2</sub> /NIV	Sepsis	Antibiotics, steroids	Italy			
X		Hospital admission	—	Chloroquine, remdesivir	Spain			
X		Admission with O <sub>2</sub> /NIV	—	Steroids, aspirin, remdesivir	USA			
		Hospital admission	Bacterial pneumonia	Antibiotics, lopinavir, ritonavir	UK			
		Hospital admission	Bacterial pneumonia	Antibiotics, chloroquine	Spain			
		Asymptomatic	Mild myocarditis	Chloroquine, lopinavir, ritonavir	Italy	Yes	41 d	
		Hospital admission	AIHA	Steroids	USA			
		Hospital admission	Bacterial pneumonia	Antibiotics	Belgium			
		Hospital admission	Multisystemic inflammatory syndrome	Antibiotics, steroids, Ig, antimycobacterial antibiotics	USA			

Pt. no.	Outcome	PID	Age group (y)	Sex	Comorbidities	Usual therapy	Manifestations					
							Fever	Cough	URS	GI	Myalgia	Other
41	Resolved	Ab def. Syndromic presentation	3-12	M	Heart defect, CD4 <sup>+</sup> T-cell lymphopenia, mental disability, dysmorphism	Ig		X	X			
42	Resolved	Ab def. CVID	13-18	M	Lung disease	Ig	X			X		
43	Resolved	Ab def. X-SCID after gene therapy, residual B- cell dysfunction ( <i>IL2RG</i> )	19-24	M	—	Ig	X	X	X	X		Anosmia, ageusia, fatigue
44	Resolved	Ab def. XLA ( <i>BTK</i> )	19-24	M	Lung disease	Ig	X	X				Dyspnea
45	Resolved	Ab def. CVID	25-34	M	IBD	Ig	X	X			X	
46	Resolved	Ab def. CVID	25-34	M	Lung disease	Ig	X	X	X		X	
47	Resolved	Ab def. CVID	25-34	F	Lung disease, AI disease	Ig, antibiotics	X	X	X			Dyspnea
48	Resolved	Ab def. CVID	25-34	M	—	Ig, antibiotics						Sore throat
49	Resolved	Ab def. CVID	25-34	M	—	Ig						Anosmia, ageusia
50	Resolved	Ab def. XLA ( <i>BTK</i> )	25-34	M	—	Ig	X	X				
51	Resolved	Ab def. APDS ( <i>PIK3R1</i> )	25-34	F	—	Ig	X					Sore throat
52	Resolved	Ab def. CVID	35-44	F	—	Antibiotics	X	X	X			
53	Resolved	Ab def. CVID ( <i>NFKB1</i> )	35-44	M	Chronic diarrhea	Ig	X	X		X		Dyspnea, fatigue
54	Resolved	Ab def. XLA ( <i>BTK</i> )	35-44	M	—	Ig	X	X				
55	Resolved	Ab def. CVID	35-44	F	Lung disease	Ig		X				
56	Resolved	Ab def CVID	35-44	F	Lung disease	Ig, antibiotics	X	X	X		X	Dyspnea, chest pain
57	Resolved	Ab def. XLA ( <i>BTK</i> )	45-54	M	Lung disease, liver disease, chronic skin and eye conditions	Ig						Asymptomatic
58	Resolved	Ab def. XLA ( <i>BTK</i> )	45-54	M	Lung disease, liver disease	Antibiotics, Ig	X			X		<i>Campylobacter jejuni</i> coinfection
59	At home	Ab def. CVID	45-54	M	Lung disease, kidney disease, GI disease	Ig, steroids, mAb	X					
60	Resolved	Ab def. CVID ( <i>NFKB1</i> )	55-64	F	Severe anemia	Ig	X	X		X		Dyspnea, fatigue
61	Resolved	Ab def. CVID	55-64	M	Lung disease, lymphoproliferative disease	Ig	X		X		X	
62	Resolved	Ab def. CVID	55-64	M	Lung disease, hypertension, splenomegaly and lymphadenopathy	Ig	X					
63	Resolved	Ab def. CVID	55-64	F	Liver disease	Ig		X				
64	Resolved	Ab def. AR agammaglobulinemia	55-64	M	Lung disease	Ig						Asymptomatic
65	Resolved	Ab def Hypogammaglobulinemia	65-74	F	Aortic coarctation	Ig	X	X	X	X	X	
66	Resolved	Ab def. CVID	65-74	F	Diabetes, hypertension, obesity	Antibiotics	X			X		
67	Resolved	Ab def. CVID	65-74	F	—	Ig, antibiotics	X	X				Dyspnea
68	At home	Ab def. CVID	65-74	F	—	—		X			X	Fatigue
69	Resolved	Ab def. CVID	65-74	F	Diabetes, obesity, hypertension	Antibiotics	X			X	X	Fatigue
70	Resolved	Ab def. IgG deficiency	≥75	M	—	Ig	X	X				Dyspnea
71	Resolved	Ab def. Hypogammaglobulinemia	≥75	F	Immune thrombocytopenia, smoker, previous breast cancer	Ig, antibiotics, ACE inhibitor, simvastatin	X	X				Infected during hospital admission for stroke
72	Resolved	CID	3-12	F	—	Antibiotics	X			X	X	
73	Resolved	CID ( <i>ZAP70</i> )	13-18	F	Lung disease, diffuse large B-cell lymphoma	Ig, rituximab, brentuximab	X	X	X			
74	Resolved	CID	13-18	F	Heart defect	Antibiotics, Ig						Asymptomatic
75	Resolved	CID	35-44	F	AIHA, thrombocytopenia, neutropenia, alopecia areata, recurrent HSV, splenomegaly	Ig, antibiotics, antivirals, rituximab						Anosmia, ageusia
76	Resolved	CID ( <i>PGM3</i> )	3-12	M	Mental disability, neutropenia, eczema	Antibiotics, antifungals, antivirals, G-CSF	X		X			
77	Resolved	CID Hyper-IgE ( <i>STAT3</i> )	25-34	M	Lung disease, hypertension	Antibiotics, antifungals					X	Headache
78	Resolved	CID Hyper-IgE ( <i>STAT3</i> )	35-44	M	GI and skin disease	Antibiotics		X				Anosmia
79	Resolved	Autoinflammation ( <i>MEFV</i> )	35-44	F	Amyloidosis	Canakinumab, colchicine	X	X	X		X	Dyspnea
80	Resolved	Autoinflammation ( <i>MEFV</i> )	45-54	F	Amyloidosis	Canakinumab, colchicine	X		X		X	
81	Resolved	Autoinflammation AGS ( <i>RNASEH2B</i> )	3-12	M	Mental disability	—						Asymptomatic
82	Resolved	Autoinflammation AGS ( <i>RNASEH2B</i> )	3-12	M	Mental disability	—						Asymptomatic
83	Resolved	Autoinflammation AGS ( <i>SAMHD1</i> )	3-12	F	Mental disability, spastic quadriplegia, epilepsy	Sodium valproate, baclofen						Rash on cheeks and arms
84	Resolved	Immune dysregulation disorder ( <i>PRKCD</i> )	3-12	M	Autoimmunity, invasive infections	Ig, sirolimus, antibiotics, hydroxychloroquine	X	X				Rhinovirus coinfection
85	Resolved	Immune dysregulation disorder Somatic ALPS	3-12	F	—	Sirolimus						Asymptomatic
86	Resolved	Immune dysregulation disorder ( <i>LRBA</i> )	19-24	M	Diabetes	Abatacept, Ig, insulin	X	X	X			
87	Resolved	Immune dysregulation APECED ( <i>AIRE</i> )	19-24	M	Lung diseases, diabetes, adrenal and thyroid insufficiency, heart disease, exocrine pancreatic insufficiency, functional asplenia	Antibiotics, antifungals, insulin, adrenal and thyroid hormones	X				X	
88	Resolved	Phagocyte defects CGD ( <i>CYBB</i> )	3-12	M	Hyporegenerative anemia	Cyclosporine, antibiotics	X		X			



Respiratory insufficiency	Invasive ventilation	Severity	Complications	Therapy	Country	Seroconversion	Estimated duration of SARS-CoV-2 PCR positivity	Duration of infection/symptoms
		Hospital admission	Incomplete HLH	Antibiotics	Germany	Yes (IgG, IgA)		7 d
		Asymptomatic	—	—	Chile			
		Hospital admission	—	—	Chile			
		Hospital admission	—	Ig, chloroquine	Mexico			
		Not admitted	—	Antibiotics	France			
		Hospital admission	—	Antibiotics, chloroquine, enoxaparin, conv. plasma	USA			
		Not admitted	—	Antibiotics, chloroquine	USA			
		NA	—	Antibiotics, chloroquine, lopinavir, ritonavir	Spain			
		Hospital admission	—	Steroids, chloroquine, enoxaparin	Brazil	No	16-35 d	
		Not admitted	—	Antibiotics	Argentina		41 d	
		Not admitted	—	—	France	Yes		2 wk
		Hospital admission	—	Antibiotics, steroids, Ig, chloroquine	Italy		64 d	
		Not admitted	—	—	USA			
		Not admitted	—	—	The Netherlands	Yes		35 d
		Hospital admission	—	Antibiotics, chloroquine, enoxaparin	USA			
		Hospital admission	—	Antibiotics, chloroquine, lopinavir, ritonavir	Italy		6-14 d	
		Not admitted	—	Antibiotics	Spain	No	6-38 d	14 d
		Hospital admission	—	Steroids, chloroquine	Brazil			
		Asymptomatic	—	—	Spain			
		Hospital admission	—	—	Spain			
		Not admitted	—	—	NA			
		Hospital admission	—	Antibiotics, chloroquine, enoxaparin	USA			
		Not admitted	—	Chloroquine	Spain			
		Hospital admission	—	Chloroquine, ivermectin, anakinra	Germany	Yes (IgM)	29 d	6 wk
		Not admitted	—	—	Germany	No	58 d	2 wk
		Asymptomatic	—	—	Italy	No	7 d	
		Not admitted	—	—	France			
		Not admitted	—	Antibiotics	France			
		Hospital admission	—	Antibiotics, chloroquine, enoxaparin, conv. plasma	USA			
		Not admitted	—	—	USA	No	>1 mo	>1 mo
		Not admitted	—	—	France	No		2 d
		Not admitted	—	Antibiotics, chloroquine, enoxaparin	USA			
		Hospital admission	—	Antibiotics	UK		15-24 d	15 d
		Hospital admission	—	Lopinavir, ritonavir	Spain	No	6 d	
		Hospital admission	—	—	France	Yes	36 d (still pos)	3 d
		Asymptomatic	—	—	Chile			
		Not admitted	—	Antibiotics	UK	Yes		3 d
		Not admitted	—	—	USA			
		Not admitted	—	—	USA			
		Not admitted	—	—	Spain	Yes		
		Not admitted	—	Steroids, chloroquine	Brazil			
		Not admitted	—	—	Brazil			
		Asymptomatic	—	—	France			
		Asymptomatic	—	—	France			
		Not admitted	—	Antibiotics, aspirin	UK	Yes		15 d
		Hospital admission	—	Antibiotics	UK			

Pt. no.	Outcome	PID	Age group (y)	Sex	Comorbidities	Usual therapy	Manifestations					
							Fever	Cough	URS	GI	Myalgia	Other
89	Resolved	Phagocyte defects CGD ( <i>NCF2</i> )	3-12	F	Lung disease	Antibiotics, antifungal						Asymptomatic
90	At home	Phagocyte defects	25-34	M	Lung disease	—		X				
91	Still in hospital	Phagocyte defects	35-44	M	—	Antibiotics, antifungals, mAb	X		X			Fatigue
92	Resolved	Phagocyte defects CGD ( <i>CYBB</i> )	45-54	M	Lung disease	Antibiotics						Anosmia
93	Resolved	STAT1 GOF	03-12	F	Lung disease	Ig						Asymptomatic
94	Resolved	GATA2 deficiency	13-18	F	Lung disease, bone marrow hypoplasia, pancytopenia	Ig, steroids, antifungals, G-CSF	X			X		Lower limbs edema, skin rash, hypotension

*Ab def.*, Antibody deficiency; *ACE*, angiotensin-converting enzyme; *AI*, autoimmune; *AIHA*, autoimmune hemolytic anemia; *ALPS*, autoimmune lymphoproliferative syndrome; *APECED*, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *conv.*, convalescent; *def.*, deficiency; *ECMO*, extracorporeal membrane oxygenation; *F*, female; *GI*, gastrointestinal; *GOF*, gain of function; *GvHD*, graft versus host disease; *IBD*, inflammatory bowel disease; *ITP*, immune thrombocytopenia; *JCV*, JC virus; *M*, male; *MSMD*, Mendelian susceptibility to mycobacterial disease; *NA*, not available; *NIV*, noninvasive ventilation; *pos.*, positive; *Pt. no.*, patient number; *Tx*, treatment; *URS*, upper respiratory symptoms; *X-SCID*, X-linked severe combined immune deficiency; *XLA*, X-linked agammaglobulinemia. Chloroquine and hydroxychloroquine are considered a single treatment group.

## Complications and mortality due to SARS-CoV-2 infection

Reported complications, as defined according to international guidelines<sup>26,27</sup> or current practice,<sup>13,14</sup> were bacterial pneumonia (n = 6), hemophagocytic lymphohistiocytosis (HLH) (n = 6), sepsis (n = 6 [7%]), MIS-C (P38, *IFNGR2*, 1%), and kidney failure (n = 5 [5%]). Two patients had sepsis and HLH. Furthermore, individual patients developed AIHA, thrombocytopenia, hyporegenerative anemia, neutropenia, myocarditis, and heart failure.

Nine patients in this cohort (7 adults and 2 children, 10%) died (Fig 1 and Table II): 4 males (0-2 years: n = 1; 13-18 years: n = 1; 35-44 years: n = 1; >75 years: n = 1), 5 females (35-44 years: n = 1; 55-64 years: n = 2; ≥75 years: n = 2). The child aged 0-2 years (P8, Table II) had X-CGD, concomitant *Burkholderia* sepsis, and HLH. The other child (P9, 13-18 years) had severe gut graft versus host disease following HSCT for *XIAP* deficiency and developed septic shock and HLH. Thus, it is unclear how much SARS-CoV-2 infection contributed to the death in both children. P1 (male, 35-44 years) suffered a syndromic disease with congenital dysmorphisms, mild developmental delay, hypogammaglobulinemia, neutropenia, hypertrophic cardiomyopathy, and bronchopathy. He developed pneumothorax, pulmonary hypertension, and heart failure after SARS-CoV-2 infection and died despite treatment with antibiotics, immunoglobulin infusion, steroids, and extracorporeal membrane oxygenation. The other deceased patients (5 females and 1 male) suffered from antibody deficiencies (CVID [P2, P3, P4, and P7]; isolated IgG deficiency [P5]; IgA and IgG<sub>2</sub> deficiency [P6]; Table II). Most patients were treated for potential bacterial coinfection or superinfection with antibiotics and extra immunoglobulin infusion.

All adult patients with PID who succumbed to SARS-CoV-2 infection had pre-existing comorbidities (Fig 1 and Table II): P1 had cardiomyopathy and developed pulmonary hypertension and heart failure; P2 had chronic kidney disease, underwent kidney transplant, and had several malignancies; all other patients were older than 55 years, and P3 had chronic lung and heart disease; P4 had chronic lung disease and developed sepsis; P5 had chronic lung, heart, and kidney disease, hypertension, and diabetes; P6 had diabetes; P7 had lymphoproliferative disease, gastrointestinal disease, and genital tract neoplasm and developed *Enterococcus faecium* sepsis. P2, P3, P5, P6, and P7 all developed hypotension and kidney failure during COVID-19. However, exact cause of COVID-19-related deaths for these patients is unknown.

## Treatments of SARS-CoV-2 infection in patients with IEI

Therapeutic strategies varied greatly and consisted of the following medications, alone or in combination: antibiotics (51%), immunoglobulin replacement (10.6%), hydroxychloroquine/chloroquine (33%), systemic steroids (21%), mAbs (8.5%, tocilizumab [n = 6] and anakinra [n = 1]), antivirals (lopinavir and ritonavir 12.7%, remdesivir 9.6%, favipiravir 1%), and enoxaparin (12.7%). Five patients (2 in ICU) received convalescent plasma and other treatments (antibiotics, chloroquine, remdesivir, steroids, enoxaparin, tocilizumab), with 4 surviving. Six patients were treated with tocilizumab, 4 in ICU, 1 of whom died of infection. (Hydroxy)chloroquine was administered to 31 patients (5 succumbed), and remdesivir to 9 patients, 5 of whom required admission to ICU and invasive ventilation, all of whom survived.

The association between outcome (alive/dead) and the onset of respiratory insufficiency, the presence of comorbidities, or the sex of the patient was not significantly different between patients who survived or patients who succumbed to SARS-CoV-2. Moreover, no correlation could be found between outcome and respiratory insufficiency, age groups, or PID type. Individual patient categories were too small to allow for multivariate analysis.

## DISCUSSION

Individuals with IEIs, and subsequent immune deficiency or immune dysregulation, are *a priori* considered an at-risk population for developing severe COVID-19 following SARS-CoV2 infection. Although a few studies have reported outcomes of SARS-CoV-2 infection in small numbers of patients with PID,<sup>19-22</sup> the impact of the COVID-19 pandemic on the broader global population of these patients has not been established. Here, we report the occurrence and course of SARS-CoV-2 infection in 94 patients with IEI. Distribution between diagnostic IEI categories reflected that of large patient registries ([esidregistry.org](https://esidregistry.org); [usidnet.org](https://usidnet.org)). Thus, patients with antibody deficiencies are the predominant group with COVID, and approximately 20% of patients had CIDs or impaired innate immunity (Fig 1).

Overall, presentation and risk factors (eg, pre-existing heart, lung, or kidney disease) for severe COVID-19 in patients with IEI seem very similar to those in the general population. Case-fatality rate was approximately 10%, in line with global data from the general population (1%-20%, Table I).<sup>1,10,28,29</sup> The mortality rate may actually be lower, because death of some patients may have

Respiratory insufficiency	Invasive ventilation	Severity	Complications	Therapy	Country	Seroconversion	Estimated duration of SARS-CoV-2 PCR positivity	Duration of infection/symptoms
		Asymptomatic	—	—	France	Yes	42 d (still pos.)	28 d
		Hospital admission	—	Antibiotics	France			
		Hospital admission	—	Antibiotics	France			
		Hospital admission	—	Antibiotics	France		<1 mo	
		Asymptomatic	—	—	UK			
		Not admitted	—	—	USA			
		Hospital admission	—	Chloroquine	Spain			
		Not admitted	—	Antibiotics	Mexico	Yes		
		Asymptomatic	—	—	Chile	Yes (IgM)		21 d
		Hospital admission	—	Antibiotics, steroids, Ig	Chile			

resulted from IEI, rather than SARS-CoV-2 infection (eg, *Burkholderia* infection in P8 [X-CGD]; severe graft versus host disease in P9 [XIAP deficiency, post-HSCT]). Thus, perhaps surprisingly, the inherent immunocompromised state of the patients studied here was generally not a predominant risk factor for severe COVID-19. Similar to some epidemiological analyses,<sup>28</sup> there was a male predominance among all patients with IEI (1.8:1), as well as those admitted to ICU (2.8:1). The sex ratio among patients with CVID with a more severe course (requiring at least oxygen) was also strongly skewed toward males (M:F, 8:5). However, there are apparent differences in the age distribution of patients with IEI affected by SARS-CoV-2 (median age, 25-34 years) as well as the frequency of ICU admissions (16%) compared with the general population (Table I).<sup>10</sup> Our study suggests that younger male patients with IEI are more likely to endure severe COVID-19 and require ICU admission. This skewing is not explained by the inclusion of X-linked disorders in this cohort (n = 13). Rather, differential levels of inflammatory mediators, T-cell responses, and/or virus-specific antibodies between infected males and females may explain the predominance of males with severe COVID-19.<sup>30</sup>

One of the key findings from our study is the identification of both redundancies in the human immune system for host defense against SARS-CoV-2 and putative mediators of immune pathology following viral infection. First, many patients with defects predominantly in the adaptive immune system (eg, defective humoral [XLA, agammaglobulinemia, persisting humoral immunodeficiency in X-SCID after gene therapy] and/or T-cell [ZAP70, PGM3, STAT3, ARPC1B mutations] responses) were either asymptomatic or had only mild disease and promptly recovered (Table II; see references 19-22). Similarly, 11 patients with CVID had mild disease and did not require hospital admission, despite several having comorbidities. Thus, certain components of adaptive immunity do not appear to be essential for controlling SARS-CoV-2 infection. Rather, these adaptive immune deficiencies may even contribute to a milder course by reducing the immune-mediated sequelae. This is consistent with findings that patients with IELs that specifically affect B- and T-cell development or function do not exhibit increased susceptibility to severe disease caused by influenza infection.<sup>31,32</sup> Our findings that

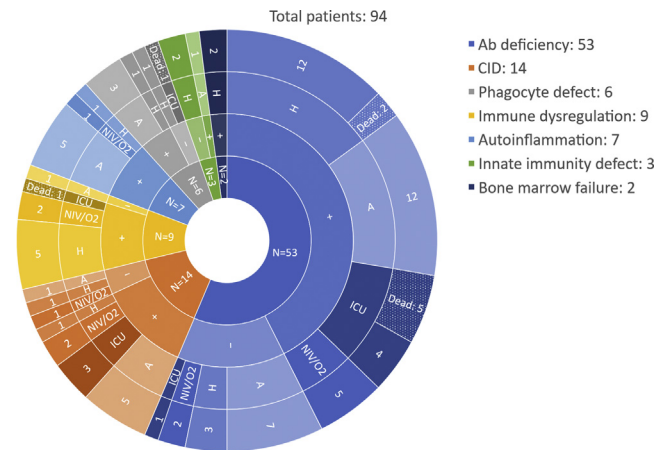
patients with CVID comprised a large proportion of our cohort (>30%), and that 4 of these patients died (45% of all deaths), may infer that intact humoral immunity is important for host defense against SARS-CoV-2. However, these patients were generally older than the rest of the cohort (median age range, 45-54 years), and many had pre-existing health conditions that predispose to severe COVID-19 in the general population (lung disease in ~50%, kidney/heart/gut/liver disease in ~20%; Table II).

Second, with the exception of the patient with X-CGD with *Burkholderia* sepsis, the other 3 patients with CGD had relatively mild disease, suggesting a modest contribution of neutrophil function in anti-SARS-CoV-2 immunity.

Third, mild or asymptomatic disease in SARS-CoV-2<sup>+</sup> patients with dominant negative STAT3 variants, despite pre-existing chronic lung disease, suggests that STAT3 signaling contributes to the cytokine storm characteristic of severe COVID-19. Together with findings that serum IL-6 levels are greatly increased during SARS-CoV-2 infection,<sup>6,33-35</sup> and predict mortality in severe COVID-19,<sup>36,37</sup> our data suggest that IL-6/STAT3 contributes to the inflammatory response and subsequent disease severity in COVID-19. Based on this, mild disease in XLA may reflect not only B-cell deficiency but also impaired IL-6 production by BTK-deficient myeloid cells,<sup>38</sup> potentially ameliorating SARS-CoV-2-induced cytokine storm.

Fourth, all patients with autoinflammatory diseases were asymptomatic or stayed at home. However, most of these patients were young children, and both adults were treated with IL-1 blockade and colchicine.

Two recent studies provide convincing evidence that disruption of type I IFN signaling is a frequent cause of life-threatening COVID-19.<sup>39,40</sup> In the first study, 650 patients with life-threatening COVID-19 were studied by whole-exome sequencing under the hypothesis that severe COVID-19 is allelic with severe influenza<sup>39</sup> or that genes biologically related to these loci would be involved.<sup>31,32</sup> Indeed, 3.5% of patients had known (AR *IRF7* and *IFNAR1* deficiency, autosomal-dominant *TLR3*, *TICAM1*, *TBK1*, and *IRF3* deficiency) and new (autosomal-dominant *UNC93B1*, *IRF7*, *IFNAR1*, and *IFNAR2* deficiency) genetic defects abolishing induction or amplification of type I IFNs.<sup>39</sup> In the second study, neutralizing autoantibodies against type I



**FIG 1.** Distribution of patients based on ICI category, comorbidities, and outcome. Shaded colors indicate patients who succumbed to COVID-19 in that ICI group. The numbers of patients (alive and deceased) are indicated for each individual subcategory on the figure. A, Ambulatory; H, hospitalized; NIV/O2, noninvasive ventilation/oxygen; "+," with comorbidities; "-", no comorbidities.

IFNs were found in 10.2% of 987 patients with life-threatening COVID-19 pneumonia, resulting in low or undetectable serum levels of IFN- $\alpha$  during acute disease; 94% of the patients with autoantibodies were male. The net result of both the anti-IFN autoantibodies and the loss-of-function variants in crucial type I IFN pathway genes is a profound defect in type I IFN immunity, underlying life-threatening COVID-19 pneumonia.

Intriguingly, we observed mild disease in patients with interferonopathies (AGS) treated with JAK inhibitors, suggesting sufficient residual type I IFN to protect from severe initial infection. It was striking that patients with *NFKB1* or *NFKB2* mutations required hospitalization, with both *NFKB2*-deficient individuals being admitted to ICU (Table II). Because the canonical and alternate *NFKB* pathways are activated in plasmacytoid dendritic cells to produce large amounts of type I IFNs,<sup>41</sup> severe COVID-19 in patients with *NFKB1* or *NFKB2* loss-of-function variants may be explained by deficient type I IFN responses. Similarly, an absence of type I IFN-producing myeloid cells may underlie COVID-19 due to *GATA2* haploinsufficiency (Table I).<sup>42</sup> Because autoimmunity is a frequent manifestation of CVID, it can be hypothesized that the presence or absence of anti-type I IFN autoantibodies predisposed patients with CVID to either life-threatening or mild disease after SARS-CoV-2 infection. The finding of neutralizing anti-IFN autoantibodies in some individuals with severe COVID-19<sup>40</sup> may also explain why patients with agammaglobulinemia generally did not develop severe COVID-19, and predict that COVID-19 may occur in some AIRE-deficient patients because these patients produce autoantibodies against type I IFNs.<sup>43</sup> Moving forward, it will be important to not only study the functionality of immune cells from patients with ICI in the context of innate IFN signaling but also assess these patients for neutralizing anti-type I IFN antibodies.

Several caveats of our study need to be recognized. First, asymptomatic or mildly symptomatic SARS-CoV-2-infected patients with ICI are likely to be underdiagnosed, mainly due to regional testing priorities contributing to an ascertainment bias of such a retrospective study. Second, because we were guided by the most recent update of ICI,<sup>16-18</sup> it is unlikely that all patients with

IEI who have been infected with SARS-CoV-2 were captured by our survey. Indeed, the field of ICI continues to grow rapidly, with more than 35 novel genetic defects having been described since the last update by the International Union of Immunological Societies committee. Thus, we have not considered SARS-CoV-2 infection in individuals with these putative novel monogenic causes of immune dysregulation. Third, if our survey accurately reflects the true incidence of COVID-19 in ICI, it suggests that immunodeficient patients have been less frequently infected and are less symptomatic than the general population. This could be explained by patients with ICI being informed early in the pandemic about safety measures by patient and scientific organizations. Moreover, patients with ICI are familiar with frequent sanitation practices, avoiding crowds, physical distancing, self-isolation, and so forth, as recommended during this pandemic. Fourth, our study does not include any patients with known defects of type I IFN pathways. On the basis of findings from studies of severe influenza,<sup>31,32</sup> and recent investigation of the genetics of life-threatening SARS-CoV-2 infection,<sup>39</sup> these patients are even more strongly advised to practice strict hand hygiene, mask wearing, and social distancing than other patients with PID.

## Conclusions

We report the course of COVID-19 in 94 patients with ICI. The survey revealed that a substantial subgroup of patients with ICI suffer only a mild course of disease. Risk factors predisposing to severe disease and mortality among patients with ICI were comparable to those in the general population. However, younger patients with ICI were more severely affected and more frequently admitted to ICU compared with the general population. These findings warrant recommendation for further stringent personal protective measures for patients affected by ICI. The urgent need to document the impact of SARS-CoV-2 on patients with defined ICI is currently being met by registries developed by additional organizations (eg, ESID registry, ERN-RITA joint effort, and COPID19), as well as the COVID Human Genetic Effort, which is performing large-scale genetic and functional studies on patients affected by severe COVID-19.<sup>15,39,40</sup> Ideally, these studies will also include prospective longitudinal analysis to determine the long-term impact of SARS-CoV-2 even in convalescent individuals. These initiatives will further our insight into susceptibility of individual patients with ICI to disease. This will not only reveal necessary and redundant pathways for host defense against SARS-CoV-2 but also identify those that mediate collateral tissue damage in response to viral infection. Collectively, this and future studies have the potential to provide opportunities for immune modulation to treat COVID-19 in patients with ICI as well as the general population.

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Membership of the International Union of Immunological Societies Committee of Inborn Errors of Immunity: Waleed Al-Herz, Aziz Bousfiha, Charlotte Cunningham-Rundles, Jose Luis Franco, Steven M. Holland, Christoph Klein, Isabelle Meyts, Tomohiro Morio, Eric Oksenhendler,



Capucine Picard, Anne Puel, Jennifer Puck, Mikko Seppanen, Raz Somech, Helen Su, Kathleen E. Sullivan, Stuart G. Tangye, and Troy R. Torgerson.

**Clinical implications: Risk factors predisposing to severe disease and mortality after SARS-CoV-2 infection in patients with IEI were similar to those in the general population. Notwithstanding inclusion and diagnostic bias, admission rates to ICU tended to be higher and median age of affected patients lower than in the general population.**

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