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 innate immune defect, 3 (3%) an antibody deficiency, 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.
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. 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. 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.

Current epidemiology studies indicate that the fatality rate of SARS-CoV-2 infection ranges from 1% to 20%, while the infection fatality rate is 0.2% to 1.3%. Despite this variability, the lethality of SARS-CoV-2 infection consistently and dramatically increases with each decade of life beyond age 50 years (Table I). Furthermore, pre-existing comorbidities (chronic lung/heart disease, obesity, diabetes, hypertension) have been reported to contribute to a more severe course of COVID-19. 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. 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.

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

Abbreviations used

AGS: Aicardi-Goutières 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
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

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infection. 

Although more than 430 monogenic IEIs have been described, the consequences of SARS-CoV-2 infection have been reported for only a few individuals with these conditions. 

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 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.

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; P4: ventricular septum defect and CD4+ 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 (bialleic variants in NCF2...
[P89] chronic granulomatous disease (CGD); 1 (P88) was treated with cyclosporin (Fig 1 and Table II). Fourteen patients had combined immunodeficiencies (CID), including 10 with syndromic features: Di George syndrome (P27); trisomy 21 (Down syndrome [P15, P17, and P26]); 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 disease (P36 and P85); and prolidase deficiency presenting feature in 11% of patients. Other reported symptoms (runny nose, sneezing: 19%) and shortness of breath/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+ 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 ≥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 [IgG2/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 |
|---------|---------|-----|---------------|-----|---------------|---------------|----------------|
| 1       | Deceased | Ab def. | 35-44 M | M | Neutropenia, dysphagia, developmental delay, hypertrophic cardiomyopathy | Ig, G-CSF | Fever, Cough, URS, GI, Myalgia, Other |
| 2       | Deceased | Ab def. | 35-44 F | F | Kidney tx, lymphoma and cervical cancer in remission | Ig, steroids | Hypotension, renal failure |
| 3       | Deceased | Ab def. | 35-44 F | F | Lung disease, heart disease, ITP | Ig, rituximab, metoprolol | Dyspnea, fatigue, hypotension, renal failure |
| 4       | Deceased | Ab def. | 35-44 F | F | Lung disease | Ig | X |
| 5       | Deceased | Ab def. | ≥75 F | M | Lung disease, heart disease, kidney disease, hypertension, diabetes | Ig | X |
| 6       | Deceased | Ab def. | ≥75 M | M | Diabetes, AIHA | Ig | X |
| 7       | Deceased | Ab def. | ≥75 F | F | Lymphoproliferative disease, GI disease, genitai tract neoplasm | Ig | Acute confusional syndrome |
| 8       | Deceased | Phagocyte defects | 0-2 M | M | — | — | Burkholderia sepsis |
| 9       | Deceased | Immune dysregulation disorder | 13-18 M | M | 4 mo post-HSCT, severe gut GVHD | Antibiotics, antifungals, Ig, steroids, cyclosporine | Collapse |
| 10      | Resolved | Ab def. | 35-44 M | M | — | Ig, antibiotics, antifungals, mAb | X, X, X |
| 11      | Resolved | Ab def. | 35-44 M | M | Lung disease | Ig, steroids, antibiotics, GM-CSF | X, X, X |
| 12      | Resolved | Ab def. | 55-64 M | M | Asthma | Ig, immunosuppressive | X, X, X |
| 13      | Resolved | Ab def. | 13-18 M | F | Aplasia tot., ptosis | — | X, X, X, X, Dyspnea |
| 14      | Resolved | Ab def. | 45-54 M | M | Lung disease | Ig, immunosuppressive | X, X |
| 15      | Resolved | CID | 3-12 M | M | Lung disease, heart disease, pulmonary hypertension, mental disability | Antibiotics, Ig, antivirals, steroids | X, X, X |
| 16      | Still in ICU | CID | 3-12 M | M | 3 mo post-HSCT, GI disease | Antibiotics, Ig, steroids | CMV encephalitis, anemia |
| 17      | Still in ICU | Wiskott-Aldrich syndrome | 0-2 M | M | Heart defect, tracheostomy with chronic ventilation | Antibiotics, Ig | X |
| 18      | Resolved | Ab def. | 3-12 M | M | Spherocytosis | Ig, X | X, X, Dyspnea, chest pain |
| 19      | Resolved | Ab def. | 25-34 F | F | — | Ig | X, X, Anosmia |
| 20      | Resolved | Ab def. | 25-34 M | M | — | Ig | X, X, X, Fatigue |
| 21      | Resolved | Ab def. | 45-54 M | M | Lung disease | Ig, antibiotics | X, X |
| 22      | Resolved | Ab def. | 45-54 M | M | Lung disease | Ig, antibiotics | X, X |
| 23      | Resolved | Ab def. | 45-54 M | M | Diabetes, heart disease, hypertension, neuropathy, mitochondrial myopathy | Ig, antibiotics, antifungals, ACE inhibitor, atorvastatin, bisoprolol, metformin, insulin | X, X, X |
| 24      | Resolved | Ab def. | 45-54 M | M | Large granular lymphocyte leukemia | Ig | X, X |
| 25      | Resolved | CID | 0-2 M | M | Eczema, cow milk protein allergy | Antibiotics, Ig | X |
| 26      | Resolved | CID | 3-12 M | M | — | — | Coinfection with Mycoplasma pneumoniae |
| 27      | Resolved | CID | 0-2 M | M | Lung disease, tracheostomy with chronic ventilation | Antibiotics, Ig | X |
| 28      | Resolved | CID/Phagocytic syndrome | 55-64 M | M | Lung disease | — | X, X, X, Dyspnea |
| 29      | Resolved | CID with immune dysregulation and autoinflammation | 35-44 M | M | Hyperviscous anemia, AIHA, intermittent renal insufficiency | Status post rituximab, steroids | Dyspnea, Confition with CoV229E |
| 30      | Resolved | Immune dysregulation disorder | 25-34 M | M | Kidney disease, mental disability | Steroids, antibiotics, antivirals, antifungals, mAb | X, X |
| 31      | Resolved | Immune dysregulation disorder | 13-18 F | F | Lung disease, post-HSCT with poor graft function | Ig, antibiotics, antivirals, antifungals, mAb | Dyspnea |
| 32      | Resolved | Immune dysregulation disorder | 25-34 M | M | Lung disease, GI disease, chronic IVC cystitis | Steroids, Ig, everolimus, abatacept | X, Anosmia, Agerusia |
| 33      | Resolved | Ab def. | 35-44 M | M | Lung disease | Antibiotics, antivirals, mAb | X, X, Dyspnea, fatigue |
| 34      | Resolved | Ab def. | 55-64 F | F | Lung disease | Antibiotics, Ig, omalizumab | Dyspnea |
| 35      | Resolved | CID | 0-2 M | M | 5 mo after gene therapy | Ig, prophylactic antivirals, pentamidine, thrombopoietin agonist | Asymptomatic |
| 36      | Resolved | Immune dysregulation disorder | 13-18 M | M | Immune thrombocytopenia | Mycophenolate, eltrombopag | X, X, Anemia, jaundice |
| 37      | Resolved | CID | 0-2 M | M | — | Ig | X, X, X, Military Mycobacterium avium confection, leukocytosis |
| 38      | Resolved | MSMD | 0-2 M | M | — | — | X, X, Increased anemia and thrombocytopenia |
| 39      | Resolved | Bone marrow failure | 3-12 M | M | Excocrine pancreas insufficiency, failure to thrive, cystopenia, bone anomalies, mental disability | Antibiotics, red blood cell transfusions | X, X, Increased anemia and thrombocytopenia |
| 40      | Resolved | Ab def. | 3-12 M | 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 |
|--------------------------|---------------------|----------|---------------|---------|---------|--------------|---------------------------------|-----------------------------|
| ECMO                     | ICU admission       | Pneumothorax, pulmonary hypertension, heart failure | Antibiotics, steroids, Ig | France |         |              |                                 |                             |
| Hospital admission       | Renal failure       | Antibiotics, chloroquine, enoxaparin, conv. plasma | USA |         |         |              |                                 |                             |
| X                        | ICU admission       | Renal failure | Antibiotics, chloroquine, enoxaparin | USA |         |              |                                 |                             |
| X                        | ICU admission       | Sepsis     | Antibiotics, steroids, tocilizumab, lopinavir, ritonavir | Italy | No     | 17 d (until death) | 17 d (until death) |                             |
| X                        | ICU admission       | Renal failure | Antibiotics, chloroquine, enoxaparin | USA |         |              |                                 |                             |
| X                        | ICU admission       | Renal failure | Antibiotics, chloroquine, enoxaparin | USA |         |              |                                 |                             |
| Hospital admission       | E. faecium sepsis, renal failure | Antibiotics, chloroquine | Spain |         |         |              |                                 |                             |
| X                        | ECMO ICU admission  | HLH        | Antibiotics, steroids | France |         |              |                                 |                             |
| X                        | ICU admission       | Sepsis, HLH | Antibiotics, Ig | Chile |         |              |                                 |                             |
| 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                        | ICU admission       | Sepsis (Candida) | Antibiotics, chloroquine, remdesivir, lopinavir, ritonavir, mAb | Italy | No     | 4 wk        |                                 |                             |
| X                        | ICU admission       | Sepsis HLH | Antibiotics, steroids, tocilizumab, remdesivir, conv. plasma | USA | Yes    | 8 d         |                                 |                             |
| X                        | ICU admission       | —          | Steroids, chloroquine, tocilizumab remdesivir, lopinavir, ritonavir | Italy | No     | 9 d         |                                 |                             |
| X                        | ICU admission       | HLH        | Antibiotics, steroids, Ig, remdesivir | Germany |         |              |                                 |                             |
| X                        | ICU admission       | Bacterial pneumonia | Steroids, Ig | Mexico |         |              |                                 |                             |
| X                        | ICU admission       | —          | —             | Chile |         |              |                                 |                             |
| X                        | Admission with O2/NIV | Bacterial pneumonia | Antibiotics, remdesivir, enoxaparin, conv plasma | USA |         |              |                                 |                             |
| X                        | Admission with O2/NIV | —          | Steroids, chloroquine, tocilizumab, lopinavir, ritonavir | Italy | No     | 9-50 d      |                                 |                             |
| X                        | Admission with O2/NIV | —          | Antibiotics, steroids | France | No     |              |                                 |                             |
| X                        | Admission with O2/NIV | —          | Antibiotics, Ig | France |         |              |                                 |                             |
| X                        | Admission with O2/NIV | —          | Antibiotics | France | Yes (IgM) | 15 d        | 2 mo                          |                             |
| X                        | Admission with O2/NIV | —          | Antibiotics | UK |         | 15 d | 18 d |                             |
| X                        | Admission with O2/NIV | —          | Antibiotics, chloroquine | Spain |         | 30 d        | 17 d |                             |
| X                        | Admission with O2/NIV | —          | Antibiotics | Mexico |         |              |                                 |                             |
| X                        | Admission with O2/NIV | —          | Antibiotics | Belgium |         |              |                                 |                             |
| X                        | Admission with O2/NIV | —          | Ig | Chile |         |              |                                 |                             |
| X                        | Admission with O2/NIV | —          | Steroids, lopinavir, ritonavir | France |         |              |                                 |                             |
| Hospital admission       | Anemia, neutropenia | Chloroquine, lopinavir, ritonavir, tocilizumab | Germany | Yes | 42 d | 13 d |                             |
| X                        | Admission with O2/NIV | Sepsis     | Antibiotics, steroids | Italy |         |              |                                 |                             |
| X                        | Hospital admission  | —          | Chloroquine, remdesivir | Spain |         |              |                                 |                             |
| X                        | Admission with O2/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

41 Resolved Ab def. Syndromic presentation 3-12 M Heart defect, CD4+ T-cell lymphopenia, mental disability, dysmorphism Ig X X

42 Resolved Ab def. CVID 13-18 M Lang disease Ig X X

43 Resolved Ab def. X-SCID after gene therapy, residual B-cell dysfunction (JEBGV) 19-24 M — Ig X X X X X Anosmia, agenesis, fatigue

44 Resolved Ab def. XLA (RTK) 19-24 M Lang disease Ig X X Dyspnea

45 Resolved Ab def. CVID 25-34 M IBD Ig X X

46 Resolved Ab def. CVID 25-34 M Lang disease Ig X X X X

47 Resolved Ab def. CVID 25-34 F Lang 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, agenesis

50 Resolved Ab def. XLA (RTK) 25-34 M — Ig X X

51 Resolved Ab def. APDS (PIK3R1) 25-34 F — Ig X Sore throat

52 Resolved Ab def. CVID 35-44 F — Antibiotics X X X

53 Resolved Ab def. CVID (NFKB1) 35-44 M Chronic diarrhea Ig X X X X Dyspnea, fatigue

54 Resolved Ab def. XLA (RTK) 35-44 M — Ig X X

55 Resolved Ab def. CVID 35-44 F Lang disease Ig X

56 Resolved Ab def. CVID 35-44 F Lang disease Ig, antibiotics X X X X Dyspnea, chest pain

57 Resolved Ab def. XLA (RTK) 45-54 M Lang disease, liver disease, chronic skin and eye conditions Ig X X X Asymptomatic

58 Resolved Ab def. XLA (RTK) 45-54 M Lang disease, liver disease Antibiotics, Ig X X Campylobacter jejuni coinfection

59 At home Ab def. CVID 45-54 M Lang disease, kidney disease, GI disease Ig, steroids, mAb X

60 Resolved Ab def. CVID (NFKB1) 55-64 F Severe anemia Ig X X X Dyspnea, fatigue

61 Resolved Ab def. CVID 55-64 F Lang disease, lymphoproliferative disease Ig X X X

62 Resolved Ab def. CVID 55-64 M Lang disease, hypertension, splenomegaly and lymphadenopathy Ig X

63 Resolved Ab def. CVID 55-64 F Liver disease Ig X

64 Resolved Ab def. AR 55-64 M Lang disease Ig Asymptomatic

65 Resolved Ab def. Hypogammaglobulinemia 65-74 F Aortic coarctation Ig 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 Diabetes, hypertension, obesity Ig, antibiotics X X X Dyspnea

68 At home Ab def. CVID 65-74 F Diabetes, obesity, hypertension Ig X X X Fatigue

69 Resolved Ab def. CVID (NFKB1) 65-74 F — Ig X X X

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 M F — Antibiotics X X X

73 Resolved CID (ZAP70) 13-18 F Lang disease, diffuse large B-cell lymphoma Ig, rituximab, brentuximab X X X

74 Resolved CID 13-18 F Heart defect Antibiotics, Ig X Asymptomatic

75 Resolved CID 35-44 F AIHA, thrombocytopenia, neutropenia, alopecia areata, recurrent HSV, splenomegaly, lymphadenopathy Ig, antibiotics, antivirals, rituximab Anosmia, agenesis

76 Resolved CID (PGM1) 3-12 M Mental disability, neutropenia, eczema Antibiotics, antifungals, antivirals, G-CSF X X

77 Resolved CID 25-34 M Lang disease, hypertension Antibiotics, antifungals X X Headache

78 Resolved Hyper-IgE (STAT1) 35-44 M GI and skin disease Antibiotics X Anosmia

79 Resolved Autoinflammation (MEFV) 35-44 F Amyloidosis Canakinumab, colchicine X X X X Dyspnea

80 Resolved Autoinflammation (MEFV) 45-54 F Amyloidosis Canakinumab, colchicine X X X

81 Resolved Autoinflammation AGS (RNASEH2B) 3-12 M Mental disability — Asymptomatic

82 Resolved Autoinflammation AGS (RNASEH2B) 3-12 M Mental disability — Asymptomatic

83 Resolved Autoinflammation AGS (SAMHD1) 3-12 F Mental disability, spastic quadriplegy, epilepsy Sodium valproate, baclofen Rash on cheeks and arms

84 Resolved Immune dysregulation disorder (PRRC2D) 3-12 M Autoimmunity, invasive infections Ig, sirolimus, antibiotics, hydroxychloroquine X X Rhinovirus coinfection

85 Resolved Immune dysregulation disorder (LRBA) 3-12 F — Sirolimus Asymptomatic

86 Resolved Immune dysregulation disorder (LBRA) 19-24 M Diabetes Abatacept, Ig, insulin X X X

87 Resolved Immune dysregulation APECED (AIM) 19-24 M Lang diseases, diabetes, adrenal and thyroid insufficiency, heart disease, exocrine pancreatic insufficiency, functional aplasia Antibiotics, antifungals, insulin, adrenal and thyroid hormones X X

88 Resolved Phagocyte defects CGD (CIITA) 3-12 M Hypoprotenerative 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, enoxaparin | Spain | |
| Hospital admission | — | Steroids, chloroquine, enoxaparin | Brazil | No | 16-35 d |
| Not admitted | — | Antibiotics | Argentina | Yes | 41 d |
| Not admitted | — | — | France | Yes | 2 wk |
| Hospital admission | — | Antibiotics, steroids, Ig, chloroquine | Italy | No | 64 d |
| Not admitted | — | — | USA | |
| Hospital admission | — | — | The Netherlands | Yes | 35 d |
| Hospital admission | — | Antibiotics, chloroquine, enoxaparin | Italy | No | 6-14 d |
| Not admitted | — | Antibiotics | Spain | No | 6-38 d |
| Hospital admission | — | Steroids, chloroquine | Brazil | No | 14 d |
| 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 |
| Not admitted | — | — | Germany | No | 58 d |
| Asymptomatic | — | — | Italy | No | 7 d |
| Not admitted | — | — | France | |
| Not admitted | — Antibiotics, chloroquine, enoxaparin, conv. plasma | France | |
| Hospital admission | — Antibiotics, chloroquine, enoxaparin, conv. plasma | USA | |
| Not admitted | — | — | USA | No | >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 | — Chloroquine | France | Yes | 36 d (still pos) | 3 d |
| Asymptomatic | — | 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 | |

**Notes:**
- HLH: Hemophagocytic lymphohistiocytosis
- Ig: Immunoglobulin
Complications and mortality due to SARS-CoV-2 infection

Reported complications, as defined according to international guidelines26,27 or current practice,13,14 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, hypoproliferative anemia, neutropenia, myocardiitis, and heart failure.

Nine patients in this cohort (7 adults and 2 children, 10%) died (Fig 1 and Table I): 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 I) 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 XIAF 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 syndrome 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 IgG2 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 Enteroococcus 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,19,22 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; usidnet.org). Thus, patients with antibody deficiencies are the predominant group with COVID, and approximately 20% of patients had CID 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).1,10,26,29 The mortality rate may actually be lower, because death of some patients may have...
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, 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, >30%), and that 4 of these patients died (45% of all deaths), despite several having comorbidities. Thus, certain components of adaptive immunity do not appear to be essential for controlling influenza infection.31-32 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+ 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,6,33-35 and predict mortality in severe COVID-19,36,37 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,38 potentially ameliorating SARS-CoV-2–induced cytokine storm.

Fourth, all patients with autoimmune inflammatory 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-19.39,40 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 influenza39 or that genes biologically related to these loci would be involved.51-52 Indeed, 3.5% of patients had known (AR F7 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.50 In the second study, neutralizing autoantibodies against type I
infection. It was striking that patients with sufficient residual type I IFN to protect from severe initial interferonopathies (AGS) treated with JAK inhibitors, suggesting underlying life-threatening COVID-19 pneumonia. Antibodies and the loss-of-function variants in crucial type I IFN to antibodies were male. The net result of both the anti-IFN autoantibodies against type 1 IFNs. Moving forward, it will be important to not only study the functionality of immune cells from individuals with severe COVID-19 but also assess these patients for neutralizing anti–type I IFN antibodies.

Conclusions

We report the course of COVID-19 in 94 patients with IEI. The survey revealed that a substantial subgroup of patients with IEI suffer only a mild course of disease. Risk factors predisposing to severe disease and mortality among patients with IEI were comparable to those in the general population. However, younger patients with IEI 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 IEI. The urgent need to document the impact of SARS-CoV-2 on patients with defined IEIs is currently being met by registries developed by additional organizations, as well as the COVID Human Genetic Effort, which is performing large-scale genetic and functional studies on patients affected by severe COVID-19. 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 IEI 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 IEI as well as the general population.

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