Brief report

A single-center experience of COVID-19 infection in patients with primary immunodeficiency

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Background: Reported outcomes in patients with primary immunodeficiency (PID) infected by coronavirus disease 2019 (COVID-19) have been variable owing to a combination of viral strain heterogeneity, differences in patient populations and health systems, and local availability of vaccination and specific COVID-19 therapies. There are few reports on the experience of Australian patients with PID during the pandemic.

Objectives: In this retrospective study, we describe the baseline characteristics and short-term outcomes of patients with PID who were infected by COVID-19 and known to the Royal Melbourne Hospital, a major tertiary center in Victoria, Australia.

Methods: Between April 2021 and April 2022, a total of 31 of 138 patients with PID were affected by COVID-19. More than half of them had 3 vaccine doses at the time of infection (which at the time was considered being fully vaccinated) and received COVID-19–targeted treatment.

Results: All of the infected patients had ambulatory disease, with no cases of morbidity or mortality. In line with the current literature, the PID subtypes described did not appear to independently predict worse outcomes.

Conclusions: Some protective factors include this cohort's relatively younger average age and its high uptake of vaccination and COVID-19 therapies. (J Allergy Clin Immunol Global 2024;3:100241.)

Key words: *Primary immunodeficiency, COVID-19 infection*

INTRODUCTION

Reports on coronavirus disease 2019 (COVID-19) infection in patients with primary immunodeficiency (PID) syndromes show variable outcomes, with differences driven by the heterogeneity of patient populations, health systems, availability of vaccination, viral prophylaxis and treatment, and strain virulence.[1-3] Comparable rates of infection-related morbidity have generally been delineated for cohorts of patients with PID and the general population, although the age distribution of patients infected with PID tended to be younger.[3-5] Most have found that different PID subtypes, with a few exceptions, were not independent risk factors for infection severity.[6,7] Rather, this is generally underpinned by advanced age and the presence of comorbidities, particularly cardiomyopathy and respiratory disease.[6]

Few reports have outlined the experience and outcomes of Australian individuals with PID during the COVID-19 pandemic. We describe short-term outcomes in a cohort of 138 adult patients with PID who were known to the Immunology and Allergy Department of Royal Melbourne Hospital, a tertiary center in Victoria, Australia.

The study examined the period from April 2021 to April 2022, which encompassed 3 local waves of COVID-19 infection, 103 days of lockdown, mask and vaccination mandates, and a strong emphasis on social distancing. Of the 176 known patients with immunodeficiency syndromes, those who were deceased, those who had secondary immunodeficiency syndromes, and those whose care had been transferred to a different hospital were excluded (n = 38). The time to follow-up ranged from 0 to 5 months, with a median of 3 months. Data were retrospectively collected via an audit of electronic medical records (EPIC Systems). Statistical analysis was performed by using linear regression on R Studio, with *P* values less than .05 considered statistically significant. Ethical approval for this study and use

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Abbreviations used
COVID-19: Coronavirus disease 2019
PID: Primary immunodeficiency
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

of patient data was granted by the Melbourne Health Research Ethics Committee (QA2023013).

RESULTS AND DISCUSSION

Of the 138 individuals with PID, 31 (22%) developed symptomatic COVID-19 infection during the study period. All recorded infections, confirmed via either a positive nasopharyngeal PCR or rapid antigen test result, occurred between November 2021 and the end of April 2022. This corresponded with local waves of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 Delta) variant between July and December 2021 and waves of Omicron subvariants, which peaked in January 2022 after staged reopening of international borders beginning in November 2021.[8]

Most subgroups of patients with PID, including antibody deficiency, combined immunodeficiency, and phagocytic and innate immunity defects, exhibit minimal differences with regard to COVID-19 infection phenotype.[6,7] However, patients with defects of type I interferon pathways or neutralizing autoantibodies against type I interferons (part of innate antiviral immunity) have been reported to experience worse outcomes.[6,9,10] Neutralizing autoantibodies against type I interferons are more common in previously healthy individuals who develop severe COVID-19 infection, and studies suggest that such antibodies increase in prevalence with patient age.[7,10] An earlier study suggested that individuals with DiGeorge syndrome and common variable immunodeficiency may be at increased risk,[5,11] but this has not been substantially corroborated in the literature.

Common variable immunodeficiency was the most prevalent PID in our infected cohort (21 of 31), uninfected cohort (75 of 107), and overall (96 of 138). Other PID subtypes in the infected group are summarized in Table I and included specific antibody deficiency, DiGeorge syndrome, activated Pi3K delta syndrome, cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) haploinsufficiency, X-linked agammaglobulinaemia, congenital lymphangiectasia with hypogammaglobulinaemia, and X-linked severe combined immunodeficiency. In line with the findings of current studies in this population, we found no apparent differences in infection severity or short-term outcomes between patients with these PID subtypes. The most frequently reported symptoms were cough and sore throat, and disease severity ranged from 1 to 3 on the World Health Organization clinical progression scale (corresponding to ambulatory mild disease). There were no cases of hospitalization or mortality during the audited period.

There were significantly more male patients among our cohort of infected patients (P =.046), as depicted in Table II. This may be partly driven by behavioral differences such as stricter social distancing. One study examining the impact of COVID-19 on the quality of life of 71 patients with PID and 31 healthy controls found that females reported higher levels of anxiety and fear about leaving the house owing to fear of infection in public places.[12] The average age of individuals in our study was 38 years in the infected group (range 20-77 years), which was significantly younger than the mean age of 48 years in the noninfected group (range 20-80 years). In all waves of the pandemic in Australia, individuals aged 80 to 89 years had the highest proportion of deaths due to COVID-19. In New South Wales, the overall case fatality ratio between November 2021 and February 2022 for those aged 80 to 89 was 3.6%, compared with well below 1% for those aged 79 or younger.[13] Therefore, the younger age of the infected cohort was likely a protective factor against adverse outcomes.

A greater proportion of patients in the infected group were noted to have a history of absolute lymphopenia ($<1.0 \times 10^9$/L) and utilize prophylactic antibiotics and immunosuppressive medications, suggesting a greater degree of immunosuppression. These differences did not reach statistical significance. Comorbidities associated with infection severity tend to be more prevalent in the population of those with PID, representing additional risk factors for infection-related complications.[3,5,6] In this cohort, the presence of comorbidities did not appear to influence short-term outcomes, and there was comparable prevalence between the infected and noninfected patient groups. Specifically, the prevalence of pulmonary disease (48% [P = .853]) and obesity and/or malnutrition (13% [P = .995]) were the same in both groups. The prevalence of cardiac disease was 6% in the infected group versus 7% in the noninfected group (P = .277), and the rates of chronic kidney disease were 0% and 7%, respectively (P = .584). The rates of malignancy history in the 2 groups were 19% and 12% (P = .434), and their respective rates of various disease were as follows: diabetes, 3% and 7% (P = .497), gastrointestinal disease, 16% and 16% (P = .812), and autoimmunity, 23% and 28% (P = .316).

COVID-19 vaccination has been shown to be efficacious in individuals at greater risk of morbidity and mortality. A retrospective cohort study of more than 2000 patients at Victorian residential aged care facilities during the Delta and Omicron waves found that vaccination reduced the odds of hospitalization by 40% and death by 43%.[14] COVID-19 mRNA vaccines in patients with PID have been shown to be safe, with studies demonstrating at least partial immune responses in most patients.[15-19] Patients in our cohort received varying combinations of the Comirnaty/BNT152b2 (Pfizer/BioNtech), Vaxzevria/ChAdOx1 (AstraZeneca), and SpikeVax/mRNA-1273 (Moderna) vaccines. Most patients in both the infected and noninfected cohorts had received at least 1 dose of an mRNA vaccine during the study period, and the rates of vaccination between the 2 cohorts were similar: 28 of 31 infected patients (90%) had at least 2 vaccine doses, and 17 of these patients (55%) had at least 3 doses, which was considered fully vaccinated at the time. In the uninfected group, 48 of 107 patients (45%) had at least 3 vaccine doses (P = .812). COVID-19–specific treatment, either sotrovimab (Xevudy [GSK]) or nirmatrelvir/ritonavir (Paxlovid [Pfizer]), was administered to 72% of infected patients within 5 days of symptom onset. Almost all of the infected patients (30 of 31 [97%]) were receiving regular immunoglobulin replacement before infection. The mean IgG troughs were satisfactory and similar between the infected and noninfected cohorts: 10.7 g/L and 9.9 g/L, respectively (P =.115). Immunoglobulin replacement therapy has been shown to promote regulatory T cell

TABLE I. Affected cohort

Type of PID	No. of patients	Mean patient age (y)	% of patients who were fully vaccinated	% of patients receiving antiviral treatment	Patients' symptom severity (WHO score)
CVID	21 (68%)	42	62 (13 of 21)	76 (16 of 21)	2-3
Specific antibody deficiency	3 (10%)	44	33 (1 of 3)	0 (0 of 1)	2
DiGeorge syndrome	1 (3%)	20	0 (0 of 1)	100 (1 of 1)	2
Activated Pi3K delta syndrome	2 (6%)	20.5	0 (0 of 1)	100 (2 of 2)	2
CTLA4 haploinsufficiency	1 (3%)	26	100 (1 of 1)	0 (0 of 1)	2
XLA	1 (3%)	27	0 (0 of 1)	0 (0 of 1)	2
Congenital lymphangiectasia with hypogammaglobulinaemia	1 (3%)	72	100 (1 of 1)	100 (1 of 1)	2
X-linked SCID	1 (3%)	25	100 (1 of 1)	100 (1 of 1)	2

CTLA4, Cytotoxic T lymphocyte–associated antigen 4; *Pi3K*, phosphatidylinositol 3-phosphate; *SCID*, severe combined immunodeficiency; *WHO*, World Health Organization; *XLA*, X-linked agammaglobulinemia.

TABLE II. Cohort demographics

Characteristic	Infected group	Noninfected group	*P* value
Age (y), interquartile range	38 (26)	48 (26)	.043
Male sex	68% (21 of 31)	38% (41 of 107)	.046
Immunoglobulin replacement therapy	97% (30 of 31)	94% (101 of 107)	.506
Prophylactic antibiotics	29% (9 of 31)	19% (20 of 107)	.569
Immunosuppressive medications	23% (7 of 31)	12% (13 of 107)	.089
History of lymphopenia	58% (18 of 31)	32% (34 of 107)	.214

populations and neutralization of autoantibodies,[20] although it has not been demonstrated to improve outcomes as a therapeutic agent in severe COVID-19.[21]

This single-center study is notable for the finding of uniformly benign short-term outcomes in an Australian cohort of patients with PID despite their underlying immunodeficiency, with no reports of hospitalization or mortality over the study period (138 patient years, encompassing periods of high community transmission). Contributing factors are presumed to include younger average age, virulence of circulating strains, and excellent engagement with vaccination and early access to and administration of targeted therapies. Further evaluation of the longer-term consequences of infection and the impact of available therapeutics, particularly with other cohorts, including older and immunocompetent groups, will be of utility to the rapidly evolving landscape of COVID-19 medicine.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: In the past 5 years, J. A. Douglass has received honoraria for educational presentations from Astra-Zeneca, GSK, Novartis, CSL; served on advisory boards for Sanofi-Aventis, Novartis, GSK, Astra-Zeneca, Immunosis, and CSL; and undertaken contracted or investigator-initiated research on behalf of GSK, Novartis, Immunosis, AstraZeneca, Sanofi-Aventis, Grifols, CSL, BioCryst, and Equilium; in addition, he has a personal superannuation shareholding in CSL and received book royalties from the book *Fast Facts: Asthma*. The rest of the authors declare that they have no relevant conflicts of interest.

The data underlying this article will be shared on reasonable request to the corresponding author. Written informed consent of participants was not obtained owing to the retrospective nature of the audit.

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