COVID-19 Infection in Patients with Humoral Immunodeficiency: A Case Series and Literature Review

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Abstract
Background: The coronavirus 2019 disease (COVID-19) has infected many individuals worldwide and continues to pose a significant threat to those with weakened immune systems. The data evaluating the clinical outcomes of patients with humoral immunodeficiencies that contract COVID-19 is limited and conflicting.
Objective: To describe the clinical outcomes of COVID-19 infections in patients with primary humoral immunodeficiency and compare results to current literature.
Methods: We conducted a retrospective cohort review on 15 patients with a humoral immunodeficiency defined as Common Variable Immunodeficiency, Specific Antibody Deficiency, or unspecified hypogammaglobulinemia, who contracted COVID-19. Severity scores were determined to evaluate the clinical outcomes of these patients.
Results: Of our 15-patient cohort, 33% of individuals with a humoral immunodeficiency infected with COVID-19 had moderate to severe disease, requiring hospitalization or resulting in death. COVID-19 mortality rate was found to be 7%. All 5 of our patients with severe COVID-19 infection had at least 1 comorbidity or risk factor.
Conclusion: Within our cohort of humoral immunodeficient patients infected with COVID-19, we found a higher rate of moderate to severe COVID-19 infection and worse clinical outcomes, particularly in patients with comorbidities or risk factors.

Keywords
coronavirus, COVID-19, SARS-CoV-2, primary, immunodeficiency, CVID

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic which was declared in March of 2020 has irreversibly changed society. This virus has been responsible for millions of deaths across the world and continues to infect the population and challenge healthcare infrastructure. Infections vary from asymptomatic to life threatening acute respiratory distress syndrome (ARDS) and organ failure. Several preexisting conditions have been linked to severe infection including cardiovascular disease, chronic kidney disease, chronic lung disease (particularly COPD), diabetes, sickle cell disease, cancer, immunosuppression, and pregnancy. Similarly, some risk factors correlated with poor outcomes with COVID-19 infection are advanced age, male gender, increased body mass index (BMI).[1] While COVID-19 research has been exponentially increasing, studies examining this virus's consequence on primary immunodeficiency patients remains conflicted.

Immunocompromised patients are more susceptible to viral, bacterial, and fungal infections. A virus responsible for a pandemic would in theory severely impact this population, however, only a handful of studies have been published describing outcomes of COVID-19 infections in patients with primary immunodeficiencies (PID).[2–15] Furthermore, these studies provide conflicting data as some publications identify an increased risk of morbidity and mortality in immunodeficient patients after contracting COVID-19.[2–4,9–12,15] Alternatively, other authors report a similar risk of

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severe COVID-19 infection in immunodeficient patients as the general population.[5–8,13,14] In our case series, we focus on primary humoral immunodeficiency limited to Common Variable Immunodeficiency (CVID), Specific Antibody Deficiency (SAD), and unspecified hypogammaglobulinemia. We aim to present a descriptive clinical analysis of COVID-19 infection outcomes in patients with known primary humoral immunodeficiency in the Midwestern United States and highlight an increased risk of severe COVID-19 infection in these patients, which differs from previous literature.[5–8,13,14]

Methods

A retrospective case review was conducted at the Allergy and Immunology Fellowship Program, University Hospitals, Cleveland Medical Center. The study was approved by the institutional review board at University Hospital, Cleveland Medical Center (STUDY20201805). Immunodeficient patients were identified for our study if they had a positive COVID-19 polymerase chain reaction test from April 2020 to January 2021 and were either receiving intravenous IgG replacement therapy (IVIG), or had an International Statistical Classification of Diseases (ICD-10) code for Common Variable Immune Deficiency (CVID). Patients were selected if they had a true primary humoral deficiency including CVID, SAD, or unspecified hypogammaglobulinemia. Chart reviews were conducted to ensure patients met the International Union of Immunological Societies (IUIS) definition of CVID and SAD. [16] Fifteen patients met these qualifications. Once the patients were selected, charts were reviewed for demographic information, past medical history, current maintenance therapies, and clinical COVID-19 disease course: including symptoms and management. A severity score was developed to classify COVID-19 infection outcomes in our patients defined as the following: 1 = outpatient management only, 2 = hospital admission, 3 = ICU and /or intubation, and 4 = death (Table 1).

Results

Fifteen patients with known humoral deficiency diagnosed with COVID-19 were included in our study (Table 2). Ages ranged from 29 to 87 years old. Six or 40% of patients in this group were over the age of 60. Ten (67%) were female

Table 1. Severity Score Defining Clinical Outcomes in Humoral Immunodeficient Patients Infected with COVID-19.

Score	Definition
1	Outpatient management only
2	Required Hospitalization
3	Required ICU level care and /or intubation
4	Death

and 5 (33%) were male. Five (33%) patients were classified as obese with a BMI of >30 and 1 (7%) was morbidly obese with BMI > 40. Eight (53%) patients had the diagnosis of CVID, and 6 (40%) had the diagnosis of SAD. Fourteen (93%) patients were receiving regularly scheduled IVIG at the time that they contracted COVID-19. Severity score percentages were as follows: 10 (67%) scored 1, 4 (27%) scored 2, and 1 (7%) scored 4 (Table S1). Thus, 5 patients or 33% were classified as having a moderate to severe COVID-19 infection. The average age of patients with a mild COVID-19 infection was 52.3 years, as opposed to those with a moderate to severe infection (Severity score of ≥2) was 70.4 years. Out of the 15 patients, 8 (53%) had at least one comorbidity/ risk factor for severe COVID-19 including hypertension (n = 3), diabetes mellitus (n = 1), COPD (n = 2) and obesity (n = 5). Ten (67%) of our patients were able to remain at home and receive outpatient management. All 5 patients with severe outcomes of COVID-19 infection had at least one comorbidity or risk factor. Conversely, out of the 10 patients with mild disease, only 3 or 30% had a comorbidity. One patient in the cohort passed away from COVID-19 after being treated in the intensive care unit (ICU) and requiring intubation. She had 2 comorbidities including HTN and COPD, and a risk factor of advanced age > 60 years.

Discussion

A current literature search provides 14 empirical publications describing COVID-19 infections in primary humoral deficiency, including six single patient case reports and eight case series/ cohorts.[2–15] Of note, 2 case reports are likely describing the same individual, therefore we treated both as a single data point.[2,3] In total, 109 patients with either CVID or hypogammaglobulinemia are included in these reports. Seven of these articles describe worse outcomes in immunodeficient patients with COVID-19, each documenting a higher percentage of severe infection requiring intubation and/or resulting in death.[2–4,9–12,15] Six out of these 7 articles, portraying more severe infections, highlight comorbid conditions being a factor.[3,4,9,10,12,15] However, exceptions have been documented, Ribeiro et al describe a 25-year-old athletic female from Brazil with CVID and no comorbidities who required mechanical ventilation and responded dramatically to COVID-19 convalescent plasma.[11] Mullur et al reported a death of a 42-year-old male with asthma and morbid obesity who had stopped IVIG treatments six months prior due to insurance issues.[4] He was found to have severely low IgG levels (117 mg/dL) at time of COVID-19 diagnosis, suggesting the importance of IgG replacement in protecting CVID patients from severe infections.

Alternatively, six studies document a milder course of COVID-19 infection in CVID patients.[5–8,13,14] Cohen et al described a cohort of ten CVID patients infected with

Table 2. Clinical Characteristics of 15 Humoral Immunodeficient Patients Diagnosed with COVID-19 Infection.

Patient	Age	Sex	BMI	Diagnosis	Medical history	Current therapies	Initial COVID-19 Symptoms	Outpatient LOI	Hosp. LOS	O2 required (days)	Severity Score	COVID-19 treatment
1	56Y	F	24.4	SAD	Asthma, nicotine dependence, AR	IVIG q4w	Fatigue, myalgia, sore throat, anosmia, ageusia	10 days	N/A	N/A	1	Antibiotics
2	41Y	F	58.2	CVID	Asthma, eczema, fibromyalgia, RA	IVIG q4w, MTX, HQC, fluticasone furoate and vilanterol, levocetirizine	Congestion, cough, anosmia	9 days	N/A	N/A	1	None
3	63Y	F	24.1	CVID	Behcet's disease, COPD, hypothyroidism, bee venom allergy	IVIG q3w, erythromycin ppx	Fever, cough, sore throat, fatigue, lip sore, decreased smell and taste	20 days	N/A	N/A	1	Antibiotics
4	63Y	F	29	CVID	Asthma, COPD, HTN, RA, depression	IVIG q3w	SOB, cough, headache, fatigue, fever	N/A	ICU: 7 days	7 days	4	Steroids, antibiotics, remdesivir convalescent plasma
5	87Y	F	31.6	unspecified hypogam..	Asthma, hepatitis C, HTN	IVIG q4w	Lethargic, cough	N/A	15 days	Still receiving O2	2	Convalescent plasma, steroids, O2
6	56Y	F	26	SAD	Sjogren's syndrome	IVIG q4w	Cough, congestion, fatigue, fever, diarrhea	Unknown	N/A	N/A	1	Azithromycin, steroids
7	54Y	F	28.6	CVID	Ehlers Danlos, POTS, unspecified rheumatological disease	Adalimumab, MTX, HQC	Diarrhea, cough, rhinorrhea, headache, fatigue	Unknown	N/A	N/A	1	Steroids
8	29Y	M	37.5	CVID	Ehlers Danlos	IVIG q4w	Cough, rhinorrhea, fever, headache, anosmia	2 days	N/A	N/A	1	Azithromycin, steroids
9	56Y	M	27	CVID	AR	IVIG, TMP-SMX	Congestion, fatigue, cough	8 days	N/A	N/A	1	None
10	73Y	F	19.7	SAD	Bronchiectasis	IVIG q4w	Fever, chills, fatigue	10 days	N/A	N/A	1	None
11	50Y	M	39.4	SAD		IVIG q4w	Fever, cough,	N/A	N/A	N/A	2	Azithromycin,

(continued)

Table 2. Continued.

Patient	Age	Sex	BMI	Diagnosis	Medical history	Current therapies	Initial COVID-19 Symptoms	Outpatient LOI	Hosp. LOS	O2 required (days)	Severity Score	COVID-19 treatment
					AR, thymic hyperplasia		SOB, chills, anosmia, loss of taste, fatigue		15 days			remdesivir; dexamethasone
12	66Y	M	31.6	CVID	Bronchiectasis	IVIG q3w, amoxicillin	Headache, fever, cough, anosmia	N/A	2 days	N/A	2	Remdesivir; cefuroxime
13	86Y	M	22.2	CVID	Asthma, bronchiectasis, HTN, aflb, DMI, hyperlipidemia	IVIG q4w	Fever, fatigue, anorexia	N/A	3 days	N/A	2	Unknown
14	55Y	F	26.2	SAD	SLE, RA	IVIG q4w, infliximab, mycophenolate, HQC, TMP-SMX	Congestion, diarrhea, lost taste and smell, fatigue	8 days	N/A	N/A	1	None
15	40Y	F	20.3	SAD	AR, nasal polyps, depression, anxiety, alcoholism	IVIG q4w, TMP-SMX ppx	Congestion and fatigue	Unknown	N/A	N/A	1	None

aflb, atrial fibrillation; *AR*, allergic rhinitis; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *CVID*, common variable immunodeficiency; *DMI*, diabetes mellitus type 1; *HCQ*, hydroxychloroquine; *HTN*, hypertension; *IVIG*, intravenous immunoglobulin; *LOI*, length of illness; *LOS*, length of stay; *MTX*, methotrexate; *POTS*, postural orthostatic tachycardia syndrome; *RA*, rheumatoid arthritis; *SAD*, specific antibody deficiency; *SLE*, systemic lupus erythematous; *SOB*, shortness of breath; *TMP-SMX*, trimethoprim-sulfamethoxazol

COVID-19 in New York City.[5] Seven of the patients were on IVIG at the time of COVID-19 diagnosis and three patients had comorbidities for severe COVID-19. Nine of the patients had mild-to-moderate symptoms and were managed outpatient. The only patient hospitalized had multiple known risk factors. None of these patients were diagnosed with pneumonia or required mechanical ventilation, and all patients recovered. Pattanaik et al reported a 27-year-old male with CVID complicated by granulomatous interstitial lung disease diagnosed with COVID-19 after showing mild symptoms who recovered fully at home.[6] Three other larger cohorts totaling 32 CVID patients described mild COVID-19 infections and courses similar to the general population.[7,8,13] Of note, 30 out of 32 patients were on IVIG or some IgG replacement regimen, again suggesting the importance of IgG replacement in this population.

On further review, age seems to be an important factor in COVID-19 severity in CVID patients. The average age of the cohorts in which COVID-19 infection was mild were lower than the cohorts which showed increased severity. For example, the average age of patients described by Cohen et al was 39.4 years, Greenmyer et al was 41 years, Marcus et al was 37.3 years, and the median age reported by Drabe et al was 50 years.[5,7,8,13] The other patients described by Pattinaik et al and Delavari et al were 27 and 12 years old respectively.[6,14] All these studies documented milder infections. Contrastingly, cohorts in which COVID-19 severity was increased, including our patients, documented a higher age average. The average age in our cohort was 58.3 years, the average age described by Ho et al was 57.7 years, and Myets et al showed a median age range of 45-54.[9,10] Shields et al, documented a median age of 54, as well as conducting a univariate analysis which showed a significant association between increasing age and mortality in patients with primary immunodeficiency.[15] The age distribution of our cohort is not comparable to the general population, however, it is comparable to the general population of PID patients. These findings suggest a correlation between age and COVID-19 severity which is likely an important factor for the variability seen in the literature thus far.

Results from our cohort of patients with primary humoral immunodeficiency infected with COVID-19 show that 33% had moderate to severe infection, and 7% had fatal outcome. Specifically, 4 patients required hospitalization but no mechanical ventilation or ICU care, and 1 patient required intubation but subsequently passed away. Comparing our results with the approximate general population mortality rate of 1.4% from an early Chinese study, we suggest that our cohort of humoral immunodeficient patients had a higher risk of severe disease.[17] Several reasons can be postulated to explain the increased severity of infections in the cohort of patients described. First, consistent with the literature, patients with comorbidities and risk factors, which include advanced age, male gender, obesity, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, sickle cell disease, cancer, immunosuppression, and pregnancy are at a higher risk for worse outcomes.[1] In the presented cohort, 100% of the 5 patients with a more severe COVID-19 infection had at least 1 comorbidity. Comparatively, of the 10 patients with milder COVID-19 infection only 30% had at least 1 comorbidity. The only patient with a fatal outcome in our cohort had 2 comorbidities including HTN and COPD, and advanced age risk factor. Advanced age risk factor was evident in our cohort as the average age of patients with moderate to severe COVID-19 was 70.4 years as opposed to 52.3 years for those with mild infection. The rate and type of comorbidities and risk factors in the cohort of PID patients treated at our practice do not differ from the general population. Severe COVID-19 infections have also been associated with autoantibodies against type 1 interferon (IFN).[18] Although genetic testing was not analyzed, searching for inborn errors of type 1 IFN in our cohort could lead to another explanation for the severe COVID-19 infections seen.

Factors intrinsic to the virus itself can also contribute to the increased severity in this cohort, as well as variability in severity of infections seen in the literature. Over the course of the pandemic, viral mutations have caused waves of increased infections. We now know that certain viral strains lead to increased infectivity or morbidity and mortality.[19,20] The majority of our patients presented during end of 2020. Variations seen in the severity of infections could possibly be due to the time the individual was infected, whether it was during the initial wave of infections in Spring of 2020 or a later wave. Variability of viral load in patients can also account for the difference in severity of COVID-19 infections. In addition, as vaccination against COVID-19 continues to increase, more individuals are protected from severe infections. This presents another reason why there might be a difference in COVID-19 severity in immunodeficient patients. However, during our time of data collection our patients had not begun vaccination.

A few limitations of this study should be noted. As a retrospective chart review, data collection is confined by the availability and existence of documented information. Incidence and prevalence were not reported because there were likely patients not identified with a positive COVID-19 test or humoral immunodeficiency diagnosis during the period of study collection. For instance, asymptomatic patients are less likely to be known and therefore documented, which could skew our results to favor more severe COVID-19 infections. Next, our cohort, as well as the majority of literature reviewed on COVID-19 and immunodeficiency, lacks pediatric data. As discussed previously, age is a significant factor in determining severity of disease, thus the addition of pediatric cases could impact outcomes. However, pediatric cases are less prevalent than adults in conditions like CVID. Lastly, the relatively small sample size prevents us from generalizing our findings and

definitively establishing outcomes in humoral immunodeficient patients who contract COVID-19.

COVID-19 is a serious disease that continues to have global ramifications. Those living with primary immunodeficiencies are at an increased risk of contracting infections and may be more susceptible to COVID-19. Prior studies on patients with CVID have shown varied outcomes among those that have contracted COVID-19. Our single center experience indicates a higher rate (33%) of moderate to severe COVID-19 infections in those with primary humoral immunodeficiency with a mortality rate of 7%. These results differ from some previous reports showing milder COVID-19 infections and could be due to the existence of comorbidities/ risk factors, variability in viral load, genetic predispositions, multifarious viral strains, and certain study limitations. Future studies with larger cohorts are necessary to continually assess COVID-19 outcomes in immunocompromised patients.

Author Contributions

Maaz Jalil DO: Conception and design of the study, data generation, analysis and interpretation of the data, and preparation and clinical revision of the manuscript.

Julianne Pietras OMS-III: Data analysis, literature search, preparation and clinical revision of the manuscript.

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Phuong Daniels OMS-II: Literature search, preparation and clinical revision of the manuscript.

Robert Hostoffer DO: Conception and design of the study, analysis and interpretation of the data, and clinical revision of the manuscript.

Declaration of Conflicting Interests

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Ethics Approval

This study was approved by the institutional review board at University Hospital, Cleveland Medical Center (STUDY20201805).

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration

Not applicable, because this article does not contain any clinical trials.

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