

COVID-19 Outcomes in Patients Undergoing B Cell Depletion Therapy and Those With Humoral Immunodeficiency States: A Scoping Review

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Abstract

The role of humoral immunity has been well established in reducing infection risk and facilitating viral clearance in patients with COVID-19. However, the relationship between specific antibody responses and severity of COVID-19 is less well understood. To address this question and identify gaps in knowledge, we utilized the methodology of a scoping review to interrogate risk of infection and clinical outcomes of COVID-19 in patients with iatrogenic and inborn humoral immunodeficiency states based on existing literature. Among patients with iatrogenic B cell depletion, particularly with agents targeting CD20, our analysis found increased risk of severe COVID-19 and death across a range of underlying disease states. Among patients with humoral inborn errors of immunity with COVID-19, our synthesis found that patients with dysregulated humoral immunity, predominantly common variable immunodeficiency (CVID), may be more susceptible to severe COVID-19 than patients with humoral immunodeficiency states due to X-linked agammaglobulinemia and other miscellaneous form of humoral immunodeficiency. There were insufficient data to appraise the risk of COVID-19 infection in both populations of patients. Our work identifies potentially significant predictors of COVID-19 severity in patients with humoral immunodeficiency states and highlights the need for larger studies to identify clinical and biologic confounders of disease severity.

1. Introduction

The host immune response to SARS-CoV-2 infection is complex and involves integration of both innate and humoral limbs [1,2]. Much attention has been focused on humoral immunity with attempts to define its clinical importance in both protecting the host from infection as well in resolving disease [2,3]. Clinical evidence supporting the effectiveness of humoral immunity to SARS-CoV-2 in these tasks include the therapeutic effects of monoclonal antibodies in facilitating the clearance of virus, particularly in those with suboptimal baseline humoral responses [4], and the strong correlation between the presence of baseline natural antibody status and reduced risk of reinfection [5]. The development of neutralizing antibodies has also been correlated with protection of de novo infection in those successfully immunized [6]. Less clear, however, is the role of specific antibody responses in recovery from COVID-19, as most investigations have demonstrated higher antibody levels in those with more severe forms of disease [7], suggesting that neutralizing antibodies may have a relatively limited impact on disease resolution.

Dissecting the precise role of humoral immunity to a viral infectious agent is daunting given that specific antibodies play numerous and interrelated roles within the integrated immune defense network [8,9]. Beyond their capacity to block viral entry, antibodies provide defense by interacting with complement and Fc receptors on a wide variety of cells; these functions have been linked to resolution of many infectious diseases [10–15]. Under other circumstances, however, specific antibodies can enhance pathology [16], and thus understanding this balance is important as we craft more effective therapeutics and vaccines.

Among the tools to help dissect and analyze the physiologic role of specific components of the immune response in humans is the examination of clinical settings where there are selective deficiencies and appraising the outcomes in the interactions with pathogens. These deficiencies can be primary, as observed in patients with inborn errors of immunity (IEI) or iatrogenic as in patients who are treated with targeted therapies directed against discrete components of the immune response [17]. The aim of this scoping review is to systematically map the empiric evidence regarding the severity of COVID-19 in patients with these deficiency states as well as to identify any existing gaps in knowledge. A scoping review was identified as the most appropriate method of knowledge synthesis as it was anticipated we would encounter substantial heterogeneity of study populations within these two broad categories as well as variability of reporting of immunologic data and outcomes. This review was designed to inform the field about the relative importance of humoral immunity in the integrated defense network with the prospects for better managing and counseling of patients so afflicted as well as providing insights into therapeutic development.

2. Methods

We utilized the methodology of a scoping review in order to investigate our overarching research question: “How do innate or iatrogenic deficiencies in humoral immunity impact clinical outcomes from COVID-19?” We followed the guidelines of Preferred Reporting Items for Systemic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) as outlined by Tricco et al. [18].

Eligibility criteria

Eligible studies included English-language literature related to COVID-19 and patients who received B cell depleting therapies or with humoral inborn errors of immunity (hIEI). Within the iatrogenic B cell depletion category of our literature search, the decision was made to include case reports and case series in order to obtain a higher degree of information about patient outcomes within each medication group than could be obtained within the larger cohort studies. In contrast, for the hIEI literature search, case reports, small-scale literature reviews, and cohort studies were included to identify all unique patients to date given the small population of hIEI patients who were infected with SARS-CoV-2.

Information sources

For iatrogenic B cell depletion articles, a PubMed search was conducted on November 18, 2020 for articles on COVID-19 (Concept 1, Supplemental data) outcomes in patients on CD19 and CD20-targeting medications (Concept 2, Supplemental data). Throughout the process of reviewing papers, relevant references within initial search results were also identified and included. During the writing process, select authors within the field also directed us to unpublished results. For hIEI articles, we conducted a PubMed search for articles on COVID-19 (Concept 1, Supplemental data) outcomes in patients with hIEIs through December 17, 2020. Keywords for hIEIs were systematically chosen using the 2019 Update of the IUIS Phenotypical Classification of Predominantly Antibody Deficiencies (Concept 3, Supplemental data).

Selection of sources of evidence

All articles were first screened by title and abstract for relevance, and studies not meeting inclusion criteria were removed. Studies were then reviewed in full, and mined for type of article, and reported outcomes.

Data charting process and data items

For all included studies, the highest level of care (outpatient, hospital ward, intensive care unit [ICU]) and clinical outcome (recovery or death) were tabulated. Parameters unique to iatrogenic B cell depletion articles that were charted included Specific B cell depleting therapy, time from last infusion, duration of symptoms, and serology status after recovery. B cell, IgG and IgM levels prior to infection were also queried, but were missing in the majority of papers and so were not included in the final report. Parameters unique to hIEI articles that were charted included demographic information (age, sex), specific diagnosis or genetic mutation and comorbid medical conditions.

3. Results

Selection and characteristics of sources of evidence

Our iatrogenic B cell depletion search yielded 102 results. Twelve articles were removed after being deemed unrelated through screening of title and abstract. An additional 40 articles were excluded for wrong study type or irrelevant outcomes. The final analysis consisted of 50 studies: 13 cohort studies and 37 small case series or case reports. Our hIEI search yielded 51 results. Opinion articles, ecologic studies, and articles unrelated to COVID-19 hIEI clinical outcomes were excluded. Seven articles were included for final analysis including three case reports [19–21], three cohort studies [22–24], and one literature review of case reports [25]. Duplicate patient reports across studies were accounted for, and only patients with clearly defined hIEIs from cohort studies were included. Table I lists a summary of the papers included in this scoping review by condition studied.

Section A. Do patients with compromised humoral immunity from iatrogenic B cell depletion therapy have greater risk of COVID-19 infection compared to the general population?

Epidemiologic studies of incidence without comparators

Six studies (4 in patients with Multiple Sclerosis (MS), 1 in patients with rheumatic disease, and 1 in patients with pediatric nephrotic syndrome) identified the incidence of SARS-CoV-2 infection among patients on B cell depleting therapies (Table II). Four of these studies Incidence rates ranged from 0-33%, and all data was collected between April and May of 2020. None of the studies provided direct comparisons to incidence rates within the general population at the time of the study data collection.

Epidemiologic studies of incidence of SARS-CoV-2 infection with comparators

Two studies of patients with multiple sclerosis compared B cell depletion therapy patients' risk of SARS-CoV-2 infection to patients with the same disease not on B cell depleting therapies (Table II). Both studies found an increased risk of infection among their patients on B cell depleting therapies compared to those not on B cell depleting therapies [26,27]. No studies of patients with rheumatic disease or nephrotic syndrome included a comparator group not on B cell depletion therapy.

Two additional studies in persons with multiple sclerosis (PwMS) reported comparisons between rates of anti-CD20 use among SARS-CoV-2 positive and negative patients. A retrospective study in Italy of 784 PwMS with suspected (n=593) or confirmed (n=191) COVID-19 found that PwMS with a suspected or confirmed SARS-CoV-2 infection were treated with Ocrelizumab at a significantly higher frequency than the general Italian PwMS population (OR=1.84,95%CI=1.31-2.56) [28], and New York study of SARS-CoV-2 positive/suspect positive PwMS noted a relatively high proportion of SARS-CoV-2 infected patients on anti-CD20 therapies (44.7%) compared with their PwMS population in which 33.1% of patients take anti-CD20 therapies [29]. Based on the data mentioned above, there are no consistent findings that iatrogenic B cell depletion increases the risk of acquiring COVID-19.

Section B: Are patients with compromised humoral immunity at risk for more severe outcomes from COVID-19 than patients with functioning humoral systems?

Iatrogenic B cell depletion – Effects on COVID-19 disease severity

Through case reports, we identified 54 individual cases of COVID-19 among patients on anti-CD20 medications (supplementary table) reporting a variety of severity variables. 74% were hospitalized (29/39), 28% were treated outpatient (11/39), and 23% were in the ICU (9/39). Their reported duration of symptoms averaged 28.8 days.

Among case series assessing severity (Table III), two clinical case series (one in PwMS and one in patients with rheumatic disease) examined the severity of COVID-19 among patients on B cell depleting therapies compared to patients not on B cell depleting therapies. Odds ratio of severe infection ranged from 2.59 (1.43-4.67) [28] and 4.34(1.77-10.63) [30] compared to patients with the same disease not on B cell depleting therapies. Among studies examining patients with rheumatic disease a recent series from a French Registry of patients, using multivariate analysis, found that rituximab use was associated with an increased risk of severe infection (defined as requiring ICU admission or death) compared to mild or moderate(defined as requiring hospital admission) (OR=4.34 (1.77–10.63)) [30]. Among the studies of PwMS, only a single study examined the influence of B cell depleting therapy on mortality in comparison to other immune based therapies, where Sormani et al. [28] found an increased risk of severe disease (defined as developing at least one of death, ICU admission, diagnosis of pneumonia, or hospitalization) among patients on anti-CD20 agents Ocrelizumab or Rituximab compared to PwMS with COVID-19 not on B cell depleting therapies adjusting for likely cofactors that could affect disease outcome (OR= 2.59 (1.43-4.67)) [28].

In terms of variables reflecting disease severity, death is the most specific. Ten case series were identified that provided mortality rates among patients on CD-20 depleting therapies with COVID-19 or suspected COVID-19 (Tables II and III). Among these, 5 studies focused on PwMS, 4 on patients with rheumatic diseases, and one in patients with cancer (Tables II and III). The number of patients on B cell depleting drugs in these series ranged from 3 to 1858 and the mortality ranged from 0 to 33% (Tables II and III).

Two studies of rheumatic diseases incorporated multivariable logistic regression analysis and a comparator group to assess risk of mortality among those with rheumatic disease on B cell depleting therapy (Table III) [30,31]. In the French Registry, the odds ratio for death among patients on rituximab compared to a matched control group was elevated (4.04, 1.35-12.04) [30]. In the largest study of patients with rheumatic disease and COVID-19, the Global Rheumatology Alliance analyzed 3729 patients (192 of which were on rituximab) and found rituximab carried the highest odds of death compared to patients on methotrexate monotherapy in both unadjusted and adjusted multivariable logistic regression models (adjusted for potential explanatory variables including other medications and comorbidities; OR 4.04, 2.32-7.03) [31]. Unfortunately, no study among PwMS provided a focused statistical analysis of mortality rates among B cell depleted patients. Thus, based upon these data with their inherent limitations it appears that iatrogenic B cell depletion may be associated with both increased risk of severe disease and risk of mortality among patients both with rheumatic disease as well as multiple sclerosis.

Humoral Inborn Errors of Immunity - Effects on COVID-19 disease severity

Our search identified 69 unique patients (37.7% female) with hIEs and confirmed SARS-CoV-2 infection from across the globe (Table IV). The majority of patients (42) had common variable immunodeficiency (CVID) [19,22–25]. Thirteen patients had agammaglobulinemia (10 X-linked, three autosomal recessive) [21–25]. Five patients had specific immunoglobulin deficiencies (IgG, IgA, or both) [20,22–24]; four patients had otherwise unspecified hypogammaglobulinemia [22,23]; two patients each had hyper-IgM disease [22,24] and antibody deficiency with syndromic features [23]; and one patient had activated PI3K delta syndrome (APDS) [23]. The age distribution of the cohort ranged from pediatric patients to the elderly (>75), though patients with agammaglobulinemia were younger on average than their CVID counterparts (no patient older than 54). Mean age could not be calculated due to incomplete data.

The risk of SARS-CoV-2 infection among patients with hIE remains incompletely understood, as most studies examined clinical outcomes in hIE patients with confirmed SARS-CoV-2 infection rather than incidence of infection. However, one large cohort study of 4718 patients with primary immunodeficiencies (PIDs) in Iran, including 1001 with hIEs alive during the pandemic, found 19 confirmed cases of SARS-CoV-2 infection, with four cases among hIE patients. Overall, the incidence of infection in this PID cohort was only 1.23 fold higher than the general population. Importantly, as the authors noted, the external validity of this may be limited due to pediatric skew of the cohort as well as increased precautions taken by patients with PIDs [24].

Within the CVID cohort (45% female) identified by our search, 10 patients (24%) required intensive care and/or mechanical ventilation. Sixteen patients were hospitalized without intensive care, and the 16 remaining patients were either asymptomatic or received outpatient care only. Treatment regimens varied from supportive care only to aggressive multidrug regimens of antibiotics, steroids, and immunomodulatory agents. Patient comorbidities also varied significantly, from none to chronic lung, liver, endocrine, cardiovascular, and kidney disease. In total, seven (16.7%) CVID patients died, all of them female. Among 12 CVID patients without notable comorbidities, one died, and among seven patients age 65 or older, two died [19,22–25].

Among 13 agammaglobulinemia patients (100% male), one patient required intensive care, nine patients were hospitalized without intensive care, and three patients were either asymptomatic or received outpatient care only. Treatment varied from supportive care only to convalescent plasma infusions, antibiotics, and immunomodulatory agents. Strikingly, although over half (7) of these patients had pre-existing comorbid lung disease (e.g., COPD, bronchiectasis), all of them recovered from COVID-19 [21–25].

Based on these limited data, it appears that patients with dysregulated humoral immune responses, such as CVID, may be more susceptible to severe COVID-19 than patients with ostensibly more severe, but select, humoral immunodeficiency states characterized by agammaglobulinemia.

4. Discussion

To the best of our knowledge, this scoping review is the first attempt to analyze and synthesize the role of humoral immunity in COVID-19 infection across a spectrum of clinical disorders caused by iatrogenic B cell depletion and inborn errors of immunity. We believe our observations have potentially important implications for understanding the network of host defense against SARS-CoV-2, but have significant limitations in their strength, as will be discussed.

Defining the precise role of humoral immunity in the integrated defense against SARS-CoV-2 infection is problematic and incompletely understood. Antibodies (specifically IgG, IgM, and IgA) have long been recognized as important components of adaptive immune defense and protection in respiratory viral infections, particularly in influenza and other human coronaviruses [8,10,13]. In COVID-19, there is now clear evidence that a SARS-CoV-2 specific antibody response is important during the early stages of infection, evidenced by the strong correlation between antibody response to vaccine and protection from incident and severe infections in non-human primate studies [32,33], the effectiveness of monoclonal antibodies [34] and convalescent plasma [35] early in infection, and the correlation between the neutralizing antibody seroconversion and multiple log reduction in viral load in cases of uncomplicated infection in humans [34].

The role of specific antibodies in latter stages of the infection is less clear, as most patients with advanced forms of COVID-19 have higher viral loads than those with mild and early disease despite higher levels of antibodies with neutralizing capacity [36,37]. Further, the same monoclonal antibody therapy effective at controlling infectious spread early in COVID-19 is not effective in later stages of disease [4].

The results of our scoping review provide insights from two disease models that both share deficits of humoral immune responsiveness: (1) iatrogenic depletion of B cells with biologic therapies and (2) primary inborn errors of immunity with explicit humoral defects. Each provide some degree of insight into the role of antibodies against SARS CoV-2.

From our examination of COVID-19 in patients with IELs, we found no studies of adequate design to assess whether patients are more susceptible to SARS-CoV-2 infection. Largely from detailed individual case reports and small series (Table IV), we did appraise evidence documenting recovery from SARS-CoV-2 infection without a significant antibody response. This evidence confirms a major role for cell mediated immunity in infection resolution [38] and is consistent with numerous reports of recovery in healthy individuals without generating detectable antibody response [7,39].

Within the IEI spectrum, our review supports a general trend for greater morbidity and mortality among patients with CVID than patients with x-linked agammaglobulinemia (XLA), an observation previously made by others [23,25]. The reasons for this differential disease severity between these subsets of IEI are unclear but several factors deserve comment. First, CVID is a highly heterogeneous immune deficiency disorder which, by definition, includes defective humoral immune function, but often is attended by variable defects within the cell mediated immune compartment as well [40,41]. In contrast, patients with XLA display defective B cell maturation with relatively preserved T cell function as reflected by relatively preserved ex vivo responses to respiratory viruses [42]. Severe COVID-19 disease is often accompanied by a state of hyperinflammation, raising the question of whether patients with CVID, who are also at elevated risk of dysregulated inflammatory and granulomatous reactions [43–45], may be predisposed to such immunodysregulation. An additional mechanistic explanation for the favorable survival rate among those with XLA may be related to the expression of BTK in macrophages and its role in TLR mediated NF- κ B triggering of the production of multiple cytokines incriminated in the hyperinflammatory phase of COVID-19 [46]. Based upon such rationale, the covalent inhibitor of BTK acalabrutinib has been used in a small open trial of 19 patients with severe COVID-19 demonstrating some degree of clinical success as well as ex vivo evidence of elevated BTK activity. The remaining forms of humoral IEI encountered in our review are too rare to draw any further conclusions regarding outcomes, though 13/17 (76%) with these miscellaneous conditions did survive (Table IV). Lastly, the patients with CVID included in this review tended to be older and had a greater burden of comorbidities, such as chronic lung disease. As we were unable to adjust for demographic differences between these two cohorts in this scoping review, it is possible these factors also underlie the observed differences in COVID-19 severity and survival.

Our review of patients with iatrogenic B cell depletion also revealed no studies of sufficient rigor to assess whether patients on such therapies are more predisposed to SARS-CoV-2 infection. In terms of disease severity in patients with iatrogenic B cell depletion states, our review suggests that such patients are at a higher risk for severe outcomes, including death, across

underlying disease states (i.e. rheumatic disorders, multiple sclerosis) (Tables II and III). While severe outcomes can potentially be attributed to numerous associated variables, such as underlying disease states, comorbidities, age, and other therapies, our review identified several studies of large numbers of patients [28,30,31] where multivariate analysis to search for such confounding was performed, adding weight to the notion that iatrogenic B cell depletion itself may be driving risk. Though the registries on which these data are based are limited by reporting bias and low granularity of data collection, these effects merit continued monitoring as patient registries grow.

While conclusions of increased risk of severe COVID-19 with B cell depletion are cautionary, they raise a number of questions as to what may belie these biologic effects. Patients on B cell depleting therapies are well documented to be at risk for serious infections [47], but the effects differ across indications (rheumatic, multiple sclerosis, hematologic etc.) [48–50]. Further, such patients have profound deficits to respond to a variety of vaccine challenges as well [51,52]. Although, patients on therapy with B cell depleting therapies have been demonstrated to generate cell mediated immune responses to the recombinant zoster vaccine [53]. Further studies with larger sample sizes and greater detail are essential.

The conclusions of this scoping review should be considered in the context of its limitations. As the indications for B cell depletion therapy are rare diseases and the prevalence of primary hIEIs is low, the number of patients included in our scoping review was limited. While larger cohort studies in patients on B cell depleting therapies enabled us to expand our observations in patients with iatrogenic humoral immune deficiencies, these cohort studies, particularly in PwMS, were often limited by a lack of comparison group and inconsistent definitions of severe COVID-19. Further, we were unable to adjust for any potential confounding factors in these patient populations (e.g. age, other pulmonary comorbidities). Few immunologic details at the individual case level were reported, so an ex vivo biomarker analysis (i.e. immunoglobulin levels to search for specific antibody response or T cell responses through detailed flow cytometry) was not possible, limiting further pathophysiologic insights. Thus, more robust studies with larger sample sizes and comparator groups as well as detailed case reports with more comprehensive immune response profiles are needed to identify the risk of severe disease and mortality due to COVID-19 in these patient populations and uncover possible pathophysiologic mechanisms.

The implications of this scoping review are several. First, from several sources, we have confirmed that some patients with profound inherited and acquired deficits of humoral immunity may recover from COVID-19, but certain subgroups of these patients may be vulnerable to more severe outcomes. As described previously [54,55] the likelihood that patients on B cell depleting therapies will make any meaningful humoral response to COVID-19 vaccination is low, in light of their suppressed response to other T cell dependent vaccines even when administered at their pharmacodynamic nadir [56]. However, it is unknown whether such patients can develop cell mediated immune responses to COVID-19 vaccinations and whether such response will confer significant protection. The same questions apply to patients with humoral IEI. While approximately 20% patients [57] with CVID on immunoglobulin replacement may serologically respond to influenza vaccine, the majority do not; the response to COVID-19 vaccination in patients with IEI merits future study. In total, the disease course of COVID-19 in patients with humoral immune deficiencies provides insight into both the role of humoral and cell mediated arms of the adaptive immune system in SARS-CoV-2 infection.

Declarations

Disclosures

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Conflicts of interest/Competing interests

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Availability of data and material

All data generated or analyzed during this study are included in this published article [and its supplementary information files]

Code availability

Not applicable

Authors' contributions

L. Calabrese and C. Calabrese developed the original idea for the article, literature search and data analysis was performed by J. Jones, A. Faruqi, and J. Sullivan. All authors were involved in the drafting and/or critically revisions of the work.

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Tables

Table I: Summary of papers included within Scoping Review

Condition Studied	Number of studies	Number of patients
Rheumatologic	8	319
Multiple Sclerosis or related	20	2393
Hematologic	10	24
Nephrotic	13	161
Vasculitis	9	9
hIEI	7	69
Totals:	67	2975

Table II: Incidence of COVID-19 among patients on CD20 depleting drugs

Disease	Drug	# Patients	Infection rate	Relative risk/ odds ratio (Infection)	Mortality rate	How positivity was determined	Date of data extraction	Reference
<i>Studies not including a comparison group</i>								
Multiple Sclerosis	Rituximab	54	7 (12.9%)		0	Symptoms	Apr-20	[58]
Multiple Sclerosis	Ocrelizumab	6	2(33%)		0			
Multiple Sclerosis	Ocrelizumab	6	0			Patient interview	Apr-20	[59]
Pediatric Nephrotic Syndrome	Anti CD20	159	0			Symptoms	Apr-20	[60]
Rheumatologic Diseases	Rituximab	76	13 (17.1%)		3 (23.1%)	Symptoms	May-20	[61]
<i>Studies including a comparison group</i>								
Multiple Sclerosis	Rituximab	285	21 (7.4%)	RR: 3.55 (CI: 1.45, 8.68)*		Symptoms	Apr-20	[26]
Multiple Sclerosis	Ocrelizumab	12	0					
Multiple Sclerosis	Rituximab	1858	38 (2.0%)	OR:1.85 (CI: 1.37-2.33)**	2 (5.3%)	Positive PCR result or compatible lung CT scan	May-20	[27]
Multiple Sclerosis	Ocrelizumab	24	1 (4.2%)	OR=2.83 (CI: .81-4.84)**	0			

*compared to patients on non-cell depleting, non-cell trafficking inhibitor DMTs

**compared to patients with same disease on non-B cell depleting therapies

Table III: Mortality Rate among COVID-19+ patients on B cell depleting therapies

Disease	Drug	# Patients	Mortality rate	Odds Ratio (Risk of mortality)	How positivity was determined	Date of data extraction	Reference
<i>Studies without a comparison group for mortality</i>							
Rheumatic Diseases	Anti CD20	3	1(33%)		Unknown	Unknown	[62]
Rheumatic Diseases	Rituximab	7	1 (14.3%)		Nasopharyngeal swabs or symptoms with compatible lung imaging and/or positive serology	Jun-20	[63]
Multiple Sclerosis	Anti CD20	34	2 (5.9%)		Health care provider	Apr-20	[29]
Multiple Sclerosis	Rituximab	5	1 (20%)		Symptoms	May-20	[28]
Multiple Sclerosis	Ocrelizumab	83	1 (1.2%)				
Cancer	Anti CD20	14	1 (7.1%)		SARS-CoV2 RT-PCR	Apr-20	[64]
<i>Studies including a comparison group for mortality</i>							
Rheumatic Diseases	Rituximab	192	42 (21.9%)	OR= 4.04 (2.32-7.03)*	Physician Report	Jul-20	[31]
Rheumatic Diseases	Rituximab	34	7 (20.6%)	OR=4.04 (1.35-12.04)**	Physician Report	May-20	[30]

*compared to patients on methotrexate

**cannot determine how the comparison group was defined. Adjusted for age and sex

Table IV: Clinical Outcomes in hIEI Patients with Confirmed COVID-19

Immunodeficiency	# of Patients (# Females)	Age Range	# Outpatient*	# Hospital Ward*	# ICU*	# Recovered	# Died	References
CVID	42 (19)	13 to 75+	16	16	10	35	7	[19,22–25]
XLA	10 (0)	10 to 54	1	9	0	10	0	[22–25]
ARA	3 (0)	35 to 64	2	0	1	3	0	[22,23]
Hypogamma, unspecified	4 (3)	3 to 75+	2	1	1	3	1	[22,23]
Ig Deficiency	5 (2)	8 to 75+	1	1	3	3	2	[20,22,23]
HIGM	2 (1)	6, 21	0	2	0	2	0	[22,24]
Syndromic Ab deficiency	2 (0)	3-12; 35 to 44	0	1	1	1	1	[23]
APDS PIK3R1	1 (1)	25-35	1	0	0	1	0	[23]
TOTAL	69 (26)		23	30	16	58	11	

Supplementary Files

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