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COVID-19 in Immunocompromised Hosts: What We Know So Far

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Summary: Based on existing data on COVID-19 among immunosuppressed patients, it appears that organ transplant and cancer patients may be at increased risk for severe disease and mortality, whereas the risk among patients with other types of immunocompromise is less clear.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused by SARS coronavirus 2 (SARS-CoV-2) has caused significant morbidity and mortality for patients and stressed healthcare systems worldwide. The clinical features and outcomes of COVID-19 among immunosuppressed patients, who are at presumed risk for more severe disease but who may also have decreased detrimental inflammatory responses, are not well characterized. We review the existing literature on COVID-19 among immunocompromised populations ranging from cancer patients and solid organ transplant recipients to patients with HIV and those receiving immunomodulatory therapy for autoimmune disease. Patients with malignancy and solid organ transplant recipients may be at increased risk of severe COVID-19 disease and death whereas for those with other types of immunocompromise, current evidence is less clear. Overall, further prospective, controlled studies are needed to determine the attributable risk of immunocompromising conditions and therapies on COVID-19 disease prognosis.

Key words: COVID-19; immunocompromised; cancer; transplant; biologics

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global pandemic with over 8 million reported cases and 400,000 deaths.[1,2] Due to impaired immune defenses from both underlying disease and treatment, immunocompromised patients with respiratory virus infection are at risk for more severe infection and increased rates of bacterial and fungal superinfection compared to their immunocompetent counterparts.[3,4] Similar concerns exist in regards to immunosuppressed patients infected with SARS-CoV-2.

However, the association between COVID-19 and intense cytokine release[5] raises the possibility that immunosuppression may actually temper the exuberant inflammatory response in this infection. Severe COVID-19 disease has features of cytokine release syndrome and secondary hemophagocytic lymphohistiocytosis seen in patients with other viral infections (SARS-CoV, Middle East Respiratory Syndrome, Epstein-Barr virus) and patients receiving chimeric antigen receptor T-cell therapy due to innate immune activation by SARS-COV-2.[6,7]

Important questions crucial to our understanding of immunocompromised patients with COVID-19 remain. Specifically, do immunocompromised patients have atypical clinical manifestations? Do immunosuppressed patients have more severe COVID-19 outcomes or conversely, are they protected from cytokine-mediated inflammation and therefore severe disease? What is the attributable risk of immunosuppression versus other comorbidities on COVID-19 severity? Improved knowledge will allow us to both better manage and counsel these vulnerable patients.

Here, we synthesize the rapidly accumulating literature on COVID-19 in a wide range of immunocompromised populations including cancer, hematologic malignancy, solid organ transplant (SOT), patients taking biologics and targeted disease modifying anti-rheumatic drugs, primary immunodeficiency, and HIV infection.

Cancer

Overall

In the early reports of COVID-19 from China, cancer patients made up a small proportion (0.9%) of COVID-19 cases,[8] but had more severe presentations (30% vs. 16%) and higher mortality (5.6% vs. 2.3%)[9] than the general population. Larger studies focused on COVID-19 in cancer patients have since been published and include case-control studies[10–13] and cohort studies[11,14–20] from China, U.S., and U.K. (**Table 1**).

Cancer patients with COVID-19 were predominantly male and older (median age 52-69 years) than non-cancer patients with COVID-19[11,12] with high rates of comorbidities

(hypertension, diabetes, heart disease, chronic kidney disease) known to be associated with severe disease.[9] Prevalence of cancer subtypes was consistent with country-level distribution of malignancy, with lung cancer being more prevalent among COVID-19 patients in China[10,14–16] whereas breast and prostate cancer were more common in the U.S.[11,17] Presenting symptoms were similar to the non-cancer population with fever, dry cough, dyspnea, and diarrhea being most frequent, though it is important to note some reports of asymptomatic infection in lung cancer patients.[21,22] Healthcare exposure was a significant risk factor for infection in both China and U.S.[11,15]

The largest study to date in this population a retrospective cohort study of 928 cancer patients from the U.S., Canada, and Spain entered into the COVID-19 and Cancer Consortium database.[19] Breast (21%) and prostate (16%) were most common solid tumors, 22% had hematologic malignancy (HM), and 39% of patients were on active cancer therapy. 40% were hospitalized, 13% were intubated, and case fatality rate (CFR) was 13% with factors statistically associated with 30-day mortality including older age (per 10 year, odds ratio (OR) 1.84), male sex (OR 1.63), having more than 2 comorbidities (OR 4.50), worse performance statues (OR 3.89), active malignancy, and receipt of azithromycin and hydroxychloroquine (OR 2.93). Another large prospective cohort study of 800 cancer patients with COVID-19 from a U.K. registry[20] reported a higher mortality rate of 23% despite a similar distribution of cancer types and proportion of patients on active cancer therapy, although it is notable that 88% of patients in this study were hospitalized. This estimate is similar to that of Chinese cohort studies of cancer patients with COVID-19 with CFRs ranging 11-21%[10,12,13,18] despite different cancer subtypes and therapies administered. Specifically, compared to studies from Western Countries, cancer patients with COVID-19 in China received more antiviral therapy (range 71-100%) and corticosteroids (range 30-54%).

Compared to COVID-19 patients without cancer, those with cancer appeared to have an increased risk for severe outcomes including intubation and death after adjusting for other COVID-19 risk factors. A case-control study from China of 232 cancer patients with COVID-19 propensity score matched to non-cancer patients by age, sex, and comorbidities found that patients with cancer were more likely to develop severe COVID-19 (OR 3.61).[13] Another smaller study from China[10] also that found that patients with malignancy had a statistically increased odds of intensive care unit (ICU) admission (OR 3.13) and mechanical ventilation (OR 2.71) after adjusting for sex and comorbidities. A case-control study of 218 New York cancer patients with COVID-19 reported an increased odds of death compared to age and sex-matched controls (OR 2.45, $p<0.01$) with a CFR of 28%.[11]

Subgroups of cancer patients who experienced disproportionately high mortality from COVID-19 included those with lung cancer (CFR 18-55%) and hematologic malignancy (CFR 33-41%).[11,15,18] Recent active therapy for cancer,[14,18,19] including immunotherapy and tyrosine kinase inhibitors,[10] was associated with worse outcomes. Additionally, individuals with cancer made up a larger proportion of COVID-19 patients in both the U.S. (6%)[17] and China (1%)[14] than in the general population, raising the possibility of an increased risk of SARS-CoV-2 acquisition.

Hematologic Malignancy

Focused literature specific to COVID-19 among hematologic malignancy (HM) patients is accumulating rapidly. The largest case series include over 10 patients from the U.K.,[23] France,[24] Spain,[25] and China[26] (**Table 1**).

An earlier study of 28 hematologic malignancy patients from Wuhan, China found that 10% were positive for COVID-19, among whom the CFR was 62%.[26] A subsequent study of 25 hematologic malignancy patients with COVID-19 from France noted that half were over 65 years and 92% had additional comorbidities (68% hypertension, 32% obesity, 25% diabetes). Clinical symptoms, laboratory findings (92% lymphopenia), and imaging findings (ground-glass opacities) were similar to those reported in general population. Of hospitalized patients, 52% developed acute respiratory distress syndrome and 33% required intubation with a mortality of 40% at one month, though the authors note that elderly patients with poor prognoses were not transferred to the ICU.[24] Another study from Spain examining 34 hematologic malignancy patients with COVID-19 (23% without positive polymerase chain reaction testing), 32% patients died. On multivariate survival analysis, active malignancy and poor Eastern Cooperative Oncology Group performance status (<2) were independent predictors of mortality.[25] Currently, the largest study is of 35 hematologic patients in the U.K., of whom 69% were receiving active therapy at the time of COVID-19 diagnosis and 40% died.[23]

Stem-cell transplant (SCT) recipients accounted for a small population of the hematologic malignancy patients in existing studies. Among the larger studies of HM patients with COVID-19, Malard *et al*. included seven patients who had undergone SCT (five autologous (auto-SCT), one allogeneic (allo-SCT), and one with both), of whom 86% survived, including the two patients with allo-SCT.[24] The majority of patients received supportive care; three

received lopinavir/ritonavir, anakinra, or a combination hydroxychloroquine, azithromycin, and tocilizumab. Martin-Moro *et al*. included one allo-SCT and two auto-SCT recipients, all of whom survived.[25] In a case series of seven SCT recipients (six allo-SCT, 1 auto-SCT) from the U.K. with COVID-19, CFR was 43% though notably one of the three deaths was not related to COVID-19.[27] An additional case report described a patient with acute myelogenous leukemia status post allo-SCT who died from COVID-19 during hospitalization for transplant.[28] Taken together, the overall CFR among SCT recipients in the literature is 27%, potentially lower than hematologic malignancy patients in general.

Among smaller case reports and series of HM patients with COVID-29, there have been reports of multiple myeloma patients treated with tocilizumab with favorable laboratory and clinical responses.[29,30] Additional reports suggest that patients with Waldenstrom's Macroglobulinemia[31] and chronic lymphocytic leukemia[32] on ibrutinib had milder clinical courses, raising the potential that decreased Bruton's tyrosine kinase Toll-like receptor and cytokine signaling may abrogate illness due to SARS-CoV-2. A recent study reported a young patient on Hodgkin's lymphoma treated with pembrolizumab who had favorable clinical course after COVID-19 infection despite concern that immune checkpoint inhibitors could worsen cytokine release and overactivate T cells, resulting more severe COVID-19 disease.[33]

In summary, cancer patients, and particularly those with lung cancer and hematologic malignancy, appear to be at higher risk for severe COVID-19 disease and mortality. A significant proportion of the patients in the literature had nosocomial acquisition, emphasizing need for strict infection control practices.

Solid Organ Transplantation

Existing literature on COVID-19 among SOT recipients consists of case series, case reports, and surveys from China, Spain, Italy, Netherlands, Iran, and the U.S (**Table 2**).

Examining the larger studies including more than 10 patients each,[34–52] SOT recipients with COVID-19 were predominantly male and older (median age 51-72 years) than the overall population of COVID-19 patients.[53] In U.S. studies reporting race/ethnicity,[34,35,39,45] significant proportions of patients were Hispanic (up to 42%)[35,45] or African American (up to 39%).[45] Comorbidities including hypertension, diabetes, cardiovascular disease, chronic kidney disease, and obesity were highly prevalent. Common presenting symptoms were fever, dry cough, and diarrhea, with most patients exhibiting lymphopenia and elevated CRP on presentation. Rates of complications including mechanical ventilation were high in most reports, including as high as 39% in a New York City study[35] and 75% in an Iran study,[44] both of kidney transplant recipients. Mortality among SOT recipients ranged significantly from 5-67%, potentially reflecting geographical differences in case number and available hospital resources. The largest study of 90 SOT recipients (kidney, lung, liver, heart, heart-kidney) from New York City reported a mortality rate of 18%.[45] Although therapies for COVID-19 among SOT recipients varied significantly by study, decreased immunosuppression was a mainstay of treatment (range 43-100%). The majority of patients in these studies (up to 90%) had antimetabolite therapy held and a smaller proportion had calcineurin inhibitor held or decreased (up 70%). Other therapies varied significantly by center and country and included hydroxychloroquine, tocilizumab, boosted protease inhibitors and intravenous immunoglobulin.

Among the smaller case series and individual case reports of COVID-19 in SOT recipients, notable findings included SOT recipients early in their post-transplant course who had

favorable outcomes.[54–57] In a small series of six patients from Italy, the three patients who died were over 10 years from transplant whereas the others who had mild disease were less than two years post-transplant.[56] However, a subsequent study documented that patients early in the post-transplant period accounted for a significant proportion (44%) of deaths among liver transplant recipients with COVID-19.[48] In addition to the significant variability in treatment, some patients who received boosted protease inhibitors experienced significant drug-drug interactions and toxicity.[58,59] Case series of up to six transplant recipients also document a favorable response among kidney transplant recipients with COVID-19 to tocilizumab.[60] While most cases of COVID-19 among SOT recipients were managed with immunosuppression reduction per above, there were several reports describing cases where immunosuppression was maintained and patients recovered.[61–63]

Of note, there have been case reports of HIV transplant patients with COVID-19. The first was of an HIV-positive kidney transplant recipient (CD4 395 cells/μL) with COVID-19 who had a mild course and did not require hospitalization.[64] Another patient with HIV (CD4 820 cells/μL) and liver transplant for hepatitis C cirrhosis was hospitalized for 5 days and required supplemental oxygen via nasal cannula, after which he made a full recovery.[65]

While there is significant heterogeneity among studies, many suggest increased disease severity and mortality among SOT recipients with COVID-19. The optimal management of these patients, including changes to immunosuppressive regimens and targeted antiviral therapy, remains unknown.

Biologics and Targeted Disease Modifying Anti-Rheumatic Drugs

Patients with various rheumatologic, dermatologic, neurologic, and gastrointestinal diseases take biologic therapies or targeted disease modifying anti-rheumatic drugs (e.g., Janus kinase (JAK) inhibitors) for immunosuppression. There have been many case reports and case series of COVID-19 in patients taking these medications (mainly biologics) for immunosuppression (**Table 3**).

Biologics for Inflammatory Bowel Disease

There have been three case series of COVID-19 in patients with inflammatory bowel disease (IBD), including a case series of 15 patients from Italy and France,[66] 12 patients from Spain,[67] and 79 patients from Italy.[68] In total, 64/106 (60%) were taking biologics (anti-TNF inhibitors, vedolizumab, or ustekinumab), symptoms were typical for COVID-19, and the incidence was similar to that in the community. There were only eight deaths, of which only one patient was taking a biologic. In the largest case series,[68] active IBD, age, and comorbidities were associated with worse outcomes, but use of biologic therapies was not. An international registry recently reported 525 COVID-19 cases in IBD patients from 33 different countries (63% were taking a biologic, 2% a JAK inhibitor): there were only 16 deaths (3%), and use of a TNF antagonist was not associated with disease severity.[69] Similarly, in a national Veterans' Affairs Health System cohort study (36 COVID-19 cases out of 37,857 IBD patients), the use of an anti-TNF agent was not associated with an increased risk of COVID-19 infection.[70]

There have been six large cross-sectional survey studies of rheumatologic patients in Italy and Spain of 162 patients,[71] 320 patients,[72] 458 patients,[73] 530 patients,[74] 959 patients,[75] and 859 patients.[76] Together, these studies revealed only 25 cases of COVID-19. Twelve of the patients required hospitalization and there were no deaths; 22 of the cases occurred in patients taking biologics of JAK-inhibitors.. One of the studies noted that the prevalence of COVID-19 in their rheumatologic cohort was similar to that in the general population.[73] Similarly, a case-control study from Boston compared 52 COVID-19 patients with rheumatologic disease (31% on biologics, 6% JAK inhibitors) to 104 comparators and found no difference in presenting symptoms, rate of hospitalization, or mortality although they did find that patients with rheumatologic disease had a higher risk of requiring ICU admission and mechanical ventilation.[77] There are also case reports of mild COVID-19 in patients taking an anti-TNF[78] and inhibitors of IL-1[79] and IL-6.[80]

The Global Rheumatology Alliance recently released its report of 600 COVID-19 patients with underlying rheumatologic disease (39% taking biologics or JAK inhibitors)[81] 46% of the patients were hospitalized and 9% died. Notably, monotherapy with a biologic or JAK inhibitor was associated with a *lower* odds of hospitalization (OR 0.46), largely driven by anti-TNF therapies.

Biologics for Dermatologic Conditions

There are multiple reports of asymptomatic or mild COVID-19 in patients taking dupilumab (IL-4/IL-13 inhibitor) for atopic dermatitis[82,83] or chronic sinusitis.[84] In patients with psoriasis, there are several case reports of mild COVID-19 in patients taking ixekizumab (IL-17 inhibitor),[85] guselkumab (IL-23 inhibitor),[86] or ustekinumab (IL-12/IL-23 inhibitor).[87,88] Similarly, there is a case series of COVID-19 in nine patients with psoriasis on various biologics (4 anti-TNF, 2 ixekizumab, 1 secukinumab, 1 ustekinumab, 1 guselkumab) where only 1 patient on an anti-TNF required hospitalization (and ICU care) and all recovered.[89] There is also a report of a patient taking guselkumab for psoriasis who developed severe disease but recovered.[87]

Combined Studies

A large case series of 86 patients from New York City with immune-mediated inflammatory disease (43% IBD, 41% rheumatologic disease, 16% psoriasis) and confirmed or highly suspected COVD-19 was recently published.[90] 72% of patients were on a biologic or JAK inhibitor, but use of these was not associated with the need for hospitalization for COVID-19. One patient died and one required ICU care, and neither was on a biologic or JAK inhibitor. Symptoms were typical of COVID and the rate of hospitalization was similar to that in the general population with COVID-19 in New York City. Similarly, a large population based study in Italy showed that patients taking biologics or JAK inhibitors (for any indication) had a similar risk for hospitalization and death than those in the general population.[91]

Anti-CD20 Antibodies

There are five reported cases of asymptomatic to mild infection in patients with multiple sclerosis taking ocrelizumab.[92–95] In addition, a case registry drawn from a pharmaceutical global safety database identified 74 confirmed COVID-19 cases in MS patients taking ocrelizumab: 35% required hospitalization, 7% required ICU care, and there were no deaths (although 35% had unknown outcomes). The data is more mixed with rituximab, however. There are three reported cases of mild disease in patients taking rituximab for granulomatosis with polyangiitis (GPA)[96] or MS,[95] but there are also reports of severe (but recovered) infection in a patient with GPA[97] as well as a fatal case in a patient taking rituximab for systemic sclerosis.[98]

In summary, the existing data do not show an increased risk of severe COVID-19 in patients taking biologic therapies or targeted disease modifying anti-rheumatic drugs. The effect of these medications in modulating the response to COVID-19, and whether they may actually be protective of severe disease, will require additional, more comprehensive studies.

Primary Immunodeficiency

A small case series described seven patients with primary immunodeficiency and COVID-19 (two with agammaglobulinemia, five with common variable immune deficiency (CVID)).[99] This series reported that the patients with CVID had a more severe course (three requiring ICU admission and one death) than those with agammaglobulinemia (who both had mild disease). The authors postulated this may be related to a role of B cells in the pathologic inflammatory response to SARS-CoV-2 since patients with agammaglobulinemia lack B cells. An additional case report describes a case of severe COVID-19 in a patient with CVID who required mechanical ventilation but fully recovered[100] (**Table 4**).

HIV

In addition to immunosuppression, people with HIV (PWH) might be at risk for more severe COVID-19 due to overlapping demographic and medical characteristics that are known risk factors for severe COVID-19 disease - for example, more than half of PWH in the United States are >50 year old and many have comorbidities such as diabetes, hypertension, and cardiovascular disease.[101] On the other hand, HIV might be protective against severe COVID-19 as immunosuppression could help tamper the cytokine storm of COVID-19 and some antiretrovirals may have theoretical activity against SARS-CoV-2. For example, tenofovir has been shown to bind to the SARS-CoV-2 RNA polymerase.[102] Although there was hope that some of the protease inhibitors might have activity against SARS-CoV-2, existing data does not support the efficacy of lopinavir/ritonavir[103] or darunavir.[104]

There have been multiple case series from around the world describing the course of COVID-19 disease in PWH[105–116] (**Table 5**). The majority of these cases were in patients with well controlled HIV; 75-100% of patients in these studies had a CD4 >200 cells/µL and the median CD4 ranged from 305 to 1068 cells/µL. In terms of disease severity, 25 to 100% of patients required hospitalization and 11-56% required ICU care. The percentage of patients who received COVID-specific therapies varied widely between studies, and included antivirals, steroids, interferon, and tocilizumab. The mortality rate ranged between 0 and 28% in most studies, with the exception of a small case series from New York City where 7 of 9 patients with COVID-19 died.[112]

In the largest case series from Spain of 51 HIV-infected patients with COVID-19, the clinical, laboratory, and radiologic parameters of COVID-19 in PWH were similar to those seen in the

general population.[108] Interestingly, the rate of tenofovir use in PWH diagnosed with COVID-19 was higher than in PWH without COVID-19, suggesting that tenofovir may not be effective for prophylaxis against COVID-19.

Conclusion

From our review of the existing literature to date, we can draw several preliminary conclusions about COVID-19 in immunocompromised patient populations. First, immunocompromised patients seem to have typical clinical manifestations of COVID-19. Second, patients with cancer and SOT recipients may be at higher risk for more severe COVID-19 disease. Third, patients taking biologics may not be at higher risk for severe disease based on current data; whether they are actually at *lower* risk of severe COVID-19 is not yet clear. Fourth, the current data in PWH are inconclusive regarding whether HIV-infection imparts a higher risk of severe disease.

It is important to acknowledge the limitations of this review. The landscape of COVID-19 research is rapidly evolving and therefore it is difficult to draw firm and durable conclusions, as clinical data will continue to accumulate swiftly. In addition, most of the literature to date consists of case reports, case series, and cohort studies, all of which have many potential sources for bias. Comprehensive studies are required at the population level to determine the role that different types of immunocompromise may play in modulation of COVID-19 disease. Future studies should aim to delineate the attributable risk of immunosuppression on disease severity (given the high prevalence of concomitant comorbidities that are known risk factors for severe COVID-19 disease) and should evaluate the role of health care disparities, access to healthcare resources, and therapeutics in determining outcomes in different immunocompromised patient populations.

CONFLICTS OF INTEREST

The authors have no conflicts of interests to disclose.

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Table 1: Summary of Studies of COVID-19 in Cancer Patients

Ref	Patient Population	Geographic Location	Study Design	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
All cancer						
14	1590 COVID-19 patients, 18 with cancer • 28% lung, 22% colorectal, 17% breast, 11% bladder	China (national)	Retrospective cohort	n/a	n/a	ICU or death (39)
15	1524 cancer patients, 12 with COVID-19 • 58% lung, 8% rectal, 8% colon, 8% breast, 8% bladder • 42% active treatment	China (Wuhan)	Retrospective cohort	Hospitalized (100) ICU (8)	n/a	Recovered (50) Died (25)
16	1276 cancer patients, 28 with COVDI-19 • 25% lung, 14% esophageal, 11% breast • 36% stage IV disease • 21% active treatment)	China (Wuhan)	Retrospective cohort	Hospitalized (100) ICU (21) Intubated (8)	Antivirals (71) IVIG (36) Steroids (54)	Recovered (36) Died (29)
17	5688 COVID-19 patients, 334 with cancer	U.S. (NY)	Retrospective cohort	Intubated (11)	n/a	Died (11)
10	105 cancer patients with COVID-19 • 21% lung, 12% GI, 10% breast, 10% thyroid, 9% blood • 14% chemotherapy within 40 days	China (Wuhan)	Case-control	Hospitalized (100) ICU (19) Intubated (10)	n/a	Died (11)
11	• 218 cancer patients with COVID-19 75% solid tumor, 25% HM	U.S. (NY)	Case-control	n/a	n/a	Died (28)
12	1575 patients with COVID-19, 52 with cancer • 19% lung, 17% breast, 10% colon, 8% cervical • 19% cancer therapy within 1 month	China (Wuhan)	Case-control	Intubated (0)	Antivirals (100) IVIG (25) Steroids (31)	Recovered (79) Died (21)
13	13077 patients with COVID-19, 232 with cancer	China (Wuhan)	Retrospective cohort	Hospitalized (10) Intubated (9)	Antivirals (79) Immunomodulator (37)	Died (20)
18	205 cancer patients with COVID-19 • 20% breast, 14% colorectal 12% lung, 11% HM • 20% cancer treatment within 4 weeks	China (Wuhan)	Retrospective cohort	ICU (15) Intubated (10)	Antivirals (94) IVIG (29) Steroids (30)	Died (20)

19	928 cancer patients with COVID-19 • 20% breast, 16% prostate, 22% HM • 39% active cancer therapy	U.S., Canada, Spain	Registry / retrospective cohort	Hospitalized (40) ICU (17) Intubated (13)	Antivirals (30)	Died (13)
20	800 cancer patients with COVID-19 • 22% HM, 19% GI, 13% breast • 35% cancer treatment within 4 weeks	U.K.	Registry / prospective cohort	Hospitalized (88) ICU (7)	n/a	Died (23)
Hematologic Malignancy						
26	128 HM patients, 13 with COVID-19	China (Wuhan)	Retrospective cohort	Hospitalized (100) Intubated (8)	Antivirals (>53*) Steroids (27)	Recovered (47) Died (53)
31	6 Waldenstrom's Macroglobulinemia patients on BTKi with COVID-19	U.S. (MA)	Case series	Hospitalized (17)	Antivirals (33) Tocilizumab (17)	Recovered (67) Died (0)
25	34 HM patients with known/suspected COVID-19	Spain	Retrospective cohort	ICU (6)	Antivirals (>85*) Tocilizumab (24) Steroids (50)	Died (32)
24	25 HM patients with COVID-19 • 28% SCT, 56% active therapy	France	Case series	Intubated (24)	Antivirals (20) Immunomodulators (16) Steroids (16)	Died (40)
117	7 MGUS patients with COVID-19	U.S. (NY)	Case series	Hospitalized (71) ICU (0) Intubated (0)	Antivirals (29)	Recovered (86) Died (14)
23	35 HM patients with COVID-19 • 69% active therapy	U.K.	Retrospective cohort	n/a	n/a	Died (40)
27	7 SCT recipients with COVID-19 • 86% allogeneic	U.K.	Case series	n/a	n/a	Died (43)
118	236 SCT recipients, 5 with COVID-19	Italy	Survey	n/a	n/a	n/a
119	530 CML patients, 5 with COVID-19	China	Survey	n/a	n/a	Recovered (80) Died (20)
120	7 MM patients with COVID-19	U.S. (WI)	Retrospective cohort	Hospitalized (71) ICU (57) Intubated (14)	Antivirals (43) Tocilizumab (0)	Recovered (43) Died (57)
32	8 CLL patients on BTKi with COVID-19	U.S. (NY)	Case series	Hospitalized (10) Intubated (0)		Died (25)

Studies with ≥5 patients included; *accurate estimate not available from published data, minimum % listed

Abbreviations: HM, hematologic malignancy; BTKi, Bruton tyrosine kinase inhibitor; MGUS, monoclonal gammopathy of uncertain significance; SCT, stem-cell transplant; CML, chronic myeloid leukemia; MM, multiple myeloma; n/a, not available; IVIG, intravenous immunoglobulin;

Table 2: Summary of Studies of COVID-19 in Solid Organ Transplant Recipients

Ref	Patient Population	Geographic Location	Study Design	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
51	18 SOT recipients with COVID-19 • 44% kidney, 33% liver, 22% heart	Spain	Case series	Hospitalized (83) ICU (11)	Antivirals (78) IVIg (11) Tocilizumab (6) IS reduction (83)	Recovered (62) Died (28)
50	10 kidney transplant recipients with COVID-19	China	Case series	Hospitalized (100) Noninvasive ventilation (30) Intubated (0)	Antivirals (100*) IVIg (70) Steroids (80) IS reduction (80)	Recovered (80) Died (10)
46	15 kidney transplant recipients with COVID-19	U.S. (NY)	Case series	Hospitalized (>80*) Intubated (27)	Antivirals (87) Tocilizumab (7) IS reduction (93)	Recovered (53) Died (7)
35	36 kidney transplant recipients with COVID-19	China (Wuhan)	Case series	Hospitalized (78) Intubated (36)	Antivirals (86) Tocilizumab (7) Lenrolinumab (21) IS reduction (86)	Recovered (38) Died (28)
45	90 SOT recipients with COVID-19 • 51% kidney, 19% lung, 14% liver, 10% heart, 6% dual	U.S. (NY)	Case series	Hospitalized (76) ICU (26)	Antivirals (>91*) Tocilizumab (21) Steroids (24) IS reduction (>88*)	Recovered (54) Died (18)
52	24 liver transplant recipients with COVID-19	Italy	Survey	ICU (13)	n/a	Died (21)
36	13 heart transplant recipients with COVID-19	U.S. (MI)	Case series	Hospitalized (100) ICU (46) Intubated (38)	Antivirals (62) Tocilizumab (23) Steroids (62)	Recovered (69) Died (15)
37	803 heart transplant recipients, 28 COVID-19 +	U.S. (NY)	Retrospective cohort	Hospitalized (79) Intubated (28)	Antivirals (78) Tocilizumab (26) Steroids (47) IS reduction (83)	Recovered (69) Died (25)
38	10 liver transplant recipients with COVID-19	Italy	Case series	n/a	Antivirals (60) Steroids (30) IS reduction (70)	Died (25)
39	132 SOT recipients tested for COVID-19, 21 positive	U.S. (TX)	Retrospective cohort	Hospitalized (67) ICU (33) Intubated (24)	Antivirals (57) Immunomodulatory (19) IS reduction (>86*)	Recovered (57) Died (5)

	• 57% kidney, 14% liver, 10% lung, 19% dual					
40	324 kidney transplant recipients ≥65 years, 16 with COVID-19	Spain	Retrospective cohort	ICU (12.5) Intubated (12.5)	Antivirals (>81*) Tocilizumab (25) Steroids (38) IS reduction (100)	Recovered (50) Died (50)
41	3581 SOT recipients, 23 with COVID-19 • 65% kidney, 13% heart, 13% lung, 4% liver, 4% dual	Netherlands	Retrospective cohort	Hospitalized (83) ICU (9) Intubated (9)	Antivirals (13) IS reduction (43)	Recovered (61) Died (22)
42	13 SOT recipients with COVID-19 • 54% liver, 31% kidney, 15% dual	Italy	Case series	Intubated (8)	Antivirals (92) Tocilizumab (15) Steroids (23) IS reduction (62)	Died (20)
43	41 kidney transplant recipients with known/suspected COVID-19	U.S. (NY)	Case series	Hospitalized (32)	IS reduction (63)	Recovered (56)
44	12 kidney transplant recipients with COVID-19	Iran	Case series	Hospitalized (100) ICU (83) Intubated (75)	Antivirals (100) Steroids (100) IS reduction (100)	Recovered (33) Died (67)

Studies with ≥10 patients included; *accurate estimate not available from published data, minimum % listed

Abbreviations: SOT, solid organ transplant; IS, immunosuppressive medication.

Table 3: Summary of Studies of COVID-19 in Patients on Biologics

Ref	Patient Population	Geographic Location	Study Design	No. COVID	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
Biologics (IBD)							
66	IBD • 80% biologics	Italy, France	Case series	15	Hospitalized (33) ICU (0)	n/a	Recovered (100)
67	IBD • 42% biologics	Spain	Case series	12	Hospitalized (67) ICU (8)	Antivirals (8)	Recovered (92) Died (8)
68	IBD • 61% biologics	Italy	Case series	79	Hospitalized (28) ICU (3)	n/a	Recovered (92) Died (8)
69	IBD • 63% biologics, 2% JAK inhibitors	International	Case registry	525	Hospitalized (31) ICU (5)	Antivirals (27) Tocilizumab (1) Steroids (2)	Recovered (95) Died (3) Unknown (2)
70	IBD	U.S. (national)	Cohort study	36	n/a	n/a	n/a
Biologics and JAK inhibitors (Rheum)							
71	Vasculitis • 50% biologics	Italy	Cross-sectional	4	Hospitalized (50)	Antivirals (50)	Recovered (100)
72	Arthritis • 75% biologics, 25% JAK inhib	Italy	Cross-sectional	4	Hospitalized (25)	n/a	Recovered (100)
73	Autoimmune disease • 0% biologics	Italy	Cross-sectional	1	ICU	Antivirals, toci	Recovered
74	Autoimmune disease • 100% biologics	Italy	Cross-sectional	3	Hospitalized (33)	n/a	Recovered (100)
75	Arthritis • 100% biologics	Spain	Cross-sectional	11	Hospitalized (55) ICU (9)	n/a	Recovered (100)
76	Autoimmune disease • 100% biologics	Italy	Cross-sectional	2	Asymptomatic (50) Hospitalized (50)	Antivirals (50)	Recovered (100)
77	Autoimmune • 31% biologics, 6% JAK	U.S. (MA)	Case-control	52	Hospitalized (44) ICU (21)	Antivirals (35) Anti-IL-6 (2)	Died (6)
78	Spondyloarthritis on anti-TNF	France	Case report	1	Hospitalized	None	Recovered
79	Periodic syndrome on canakinumab	Greece	Case report	1	Outpatient	None	Recovered
80	Systemic sclerosis on tocilizumab	Switzerland	Case report	1	Outpatient	None	Recovered

81	Autoimmune disease • 39% biologic or JAK	International	Case registry	600	Hospitalized (46)	n/a	Died (9%)
Biologics (Derm)							
82	Atopic dermatitis on dupilumab	Italy	Case series	2	Hospitalized (50)	Antivirals (50)	Recovered (100)
83	Atopic dermatitis on dupilumab	Italy	Case report	1	Asymptomatic	None	Recovered
84	Chronic sinusitis on dupilumab	Germany	Case report	1	Outpatient	None	Recovered
85	Psoriasis on ixekizumab	Italy	Case report	1	Asymptomatic	None	Recovered
86	Psoriasis on guselkumab	Italy	Case report	1	Outpatient	None	Recovered
87	Psoriasis on guselkumab or ustekinumab	Italy	Case series	2	Outpatient (50), ICU (50)	None	Recovered (100)
88	Psoriasis on anti-TNF or ustekinumab	U.S. (CA)	Case series	2	Outpatient (100)	None	Recovered (100)
89	Psoriasis • 100% biologics	Italy	Case series	9	Hospitalized (11), ICU (11)	n/a	Recovered (100)
Biologics, JAK inhibitors (Combined)							
90	Autoimmune disease • 43% IBD, 41% rheum, 16% psoriasis • 72% biologic or JAK	U.S. (NY)	Case series	86	Hospitalized (16), ICU (1)	Antivirals (12), Tocilizumab (1)	Recovered (99) Died (1)
91	Patients taking biologics, tsDMARDs	Italy	Population study	9	Hospitalized (44)	n/a	Died (11)
Anti-CD20 Abs							
92	MS on ocrelizumab	Italy	Case report	1	Hospitalized	None	Recovered
93	MS on ocrelizumab	France	Case report	1	Asymptomatic	None	Recovered
94	MS on ocrelizumab	Iran	Case report	1	Outpatient	None	Recovered
121	MS on ocrelizumab	International	Case registry	74	Hospitalized (35), ICU (7)	n/a	Recovered (65) Died (0) Unknown (35)
97	GPA on rituximab	France	Case report	1	ICU	Antivirals	Recovered
98	SSc on rituximab	Italy	Case report	1	ICU	Tocilizumab	Died
96	GPA on rituximab	Switzerland	Case report	1	Hospitalized	None	Recovered
95	MS • 50% ocrelizumab, 50% rituximab	Spain	Case series	4	Hospitalized (25)	n/a	Recovered (100)

Abbreviations: GPA, granulomatosis with polyangiitis; IBD, inflammatory bowel disease; MS, multiple sclerosis; SSc, systemic sclerosis; VA, Veterans' Affairs Healthcare System.

Table 4: Summary of Studies of COVID-19 in Patients with Primary Immunodeficiency

Ref	Patient Population	Geographic Location	Study Design	No. COVID	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
99	XLA, ARA, CVID	Italy	Case series	7	Asymptomatic (14) Hospitalized (86) ICU (43)	Antivirals (100) Tocilizumab (43) IVIG (100)	Recovered (86) Died (14)
100	CVID	U.S. (OH)	Case report	1	ICU	IVIG	Recovered

Abbreviations: XLA, X-linked agammaglobulinemia; ARA, autosomcal recessive agammaglobulinemia; CVID, common variable immunodeficiency

Table 5: Summary of Studies of COVID-19 in HIV Patients

Ref	Patient Population	Geographic Location	Study Design	No. COVID	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
105	HIV Median CD4 592	Italy	Case series	3	Hospitalized (100) ICU (33)	Antivirals (100) Tocilizumab (33)	Recovered (100)
106	HIV CD4>200 in 80% Median CD4 604	Spain	Case series	5	Hospitalized (100) ICU (40)	Antivirals (80) IFN (40)	Recovered (80)
109	HIV CD4>200 in 75% Median CD4 422	Turkey	Case series	4	Hospitalized (100) ICU (25)	Antivirals (75)	Recovered (75) Died (25)
110	HIV CD4>200 in 97% Mean CD4 636	Italy	Case series	47	Hospitalized (28) ICU (4)	Antivirals (30) Tocilizumab (4)	Recovered (96) Died (4)
111	HIV Median CD4 395	UK	Case series	18	Hospitalized (100) ICU (28)	Antivirals (22)	Recovered (67) Died (28)
112	HIV CD4>200 in 78% Median CD4 504	U.S. (NY)	Case series	9	Hospitalized (100) ICU (56)	Antivirals (44)	Recovered (22) Died (78)
113	HIV CD4>200 in 100% Median CD4 305	U.S. (IL)	Case series	5	Hospitalized (100) ICU (20)	Antivirals (40)	Recovered (100)
114	HIV CD4 >200 in 94% Median CD4 670	Germany	Case series	33	Hospitalized (42) ICU (18)	n/a	Recovered (91) Died (9)
115	HIV CD4>200 in 80% Mean CD4 396	U.S. (NY)	Case series	31	Hospitalized (100) ICU (23)	Antivirals (77) Steroids (26) Tocilizumab (7)	Recovered (68) Died (26)
116	HIV CD4>200 in 100% Median CD4 1068	U.S. (NY)	Case series	4	Hospitalized (25)	None	Recovered (100)
107	HIV Median CD4 551	U.S. (NJ)	Case series	27	Hospitalized (49), ICU (11)	Antivirals (26) Steroids (4)	Recovered (93) Died (7)
108	HIV CD4>200 in 88% Median CD4 565	Spain	Case series	51	Hospitalized (55) ICU (12)	Antivirals (59) Steroids (29) Tocilizumab (8)	Recovered (86) Died (4)