

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

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome 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 of 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 patients with cancer 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.

**Keywords.** COVID-19; immunocompromised; cancer; transplant; biologics.

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 of more severe infection and increased rates of bacterial and fungal superinfection compared with their immunocompetent counterparts [3, 4]. Similar concerns exist with regard 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 patients with cancer or hematologic malignancy, solid-organ transplant (SOT) recipients, patients taking biologics and targeted disease-modifying antirheumatic drugs, patients with primary immunodeficiency, and patients with human immunodeficiency virus (HIV) infection.

## Cancer

### Overall

In the early reports of COVID-19 from China, patients with cancer 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 patients with cancer have since been published and include case-control studies [10–13] and cohort studies [11, 14–20] from China, the United States, and the United Kingdom (Table 1).

Patients with cancer with COVID-19 were predominantly male and older (median age, 52–69 years) than patients without cancer 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 patients with COVID-19 in

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**Table 1. Summary of Studies of COVID-19 in Patients With Cancer**

Ref	Patient Population	Geographic Location	Study Design	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
<b>All cancer</b>						
[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 COVID-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	United States (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	United States (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]	13 077 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	United States, 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	United Kingdom	Registry/prospective cohort	Hospitalized (88), ICU (7)	n/a	Died (23)
<b>Hematologic malignancy</b>						
[21]	128 HM patients, 13 with COVID-19	China (Wuhan)	Retrospective cohort	Hospitalized (100), intubated (8)	Antivirals (>53 <sup>a</sup> ), steroids (27)	Recovered (47), died (53)
[22]	6 Waldenstrom's macroglobulinemia patients on BTKi with COVID-19	United States (MA)	Case series	Hospitalized (17)	Antivirals (33), tocilizumab (17)	Recovered (67), died (0)
[23]	34 HM patients with known/suspected COVID-19	Spain	Retrospective cohort	ICU (6)	Antivirals (>85 <sup>a</sup> ), 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)
[25]	7 MGUS patients with COVID-19	United States (NY)	Case series	Hospitalized (71), ICU (0), intubated (0)	Antivirals (29)	Recovered (86), died (14)
[26]	35 HM patients with COVID-19 • 69% active therapy	United Kingdom	Retrospective cohort	n/a	n/a	Died (40)
[27]	7 SCT recipients with COVID-19 • 86% allogeneic	United Kingdom	Case series	n/a	n/a	Died (43)
[28]	236 SCT recipients, 5 with COVID-19	Italy	Survey	n/a	n/a	n/a
[29]	530 CML patients, 5 with COVID-19	China	Survey	n/a	n/a	Recovered (80), died (20)
[30]	7 MM patients with COVID-19	United States (WI)	Retrospective cohort	Hospitalized (71), ICU (57), intubated (14)	Antivirals (43), tocilizumab (0)	Recovered (43), died (57)
[31]	8 CLL patients on BTKi with COVID-19	United States (NY)	Case series	Hospitalized (10), intubated (0)	...	Died (25)

Studies with ≥5 patients included.

Abbreviations: COVID-19, coronavirus disease 2019; GI, gastrointestinal; HM, hematologic malignancy; BTKi, Bruton tyrosine kinase inhibitor; ICU, intensive care unit; IVIG, intravenous immunoglobulin; MGUS, monoclonal gammopathy of uncertain significance; SCT, stem-cell transplant; CML, chronic myeloid leukemia; MM, multiple myeloma; n/a, not available; Ref, reference.

<sup>a</sup>Accurate estimate not available from published data, minimum % listed.

China [10, 14–16], whereas breast and prostate cancers were more common in the United States [11, 17]. Presenting symptoms were similar to the noncancer population, with fever, dry cough, dyspnea, and diarrhea being most frequent, although it is important to note some reports of asymptomatic infection in patients with lung cancer [32, 33]. Healthcare exposure was a significant risk factor for infection in both China and United States [11, 15].

The largest study to date in this population was a retrospective cohort study of 928 patients with cancer from the United States, Canada, and Spain, entered into the COVID-19 and Cancer Consortium database [19]. Breast (21%) and prostate (16%) were the most common solid tumors, 22% had hematologic malignancy (HM), and 39% of patients were on active cancer therapy. Forty percent were hospitalized, 13% were intubated, and the case-fatality rate (CFR) was 13%, with factors statistically associated with 30-day mortality including older age (per 10 years; odds ratio [OR], 1.84), male sex (OR, 1.63), having more than 2 comorbidities (OR, 4.50), worse performance status (OR, 3.89), active malignancy, and receipt of azithromycin and hydroxychloroquine (OR, 2.93). Another large prospective cohort study of 800 patients with cancer with COVID-19 from a UK 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 patients with cancer with COVID-19 with CFRs ranging from 11% to 21% [10, 12, 13, 18] despite different cancer subtypes and therapies administered. Specifically, compared with studies from Western countries, patients with cancer with COVID-19 in China received more antiviral therapy (range, 71–100%) and corticosteroids (range, 30–54%).

Compared with patients without cancer with COVID-19, those with cancer appeared to have an increased risk of severe outcomes including intubation and death after adjusting for other COVID-19 risk factors. A case-control study from China of 232 patients with cancer with COVID-19 propensity score matched to patients without cancer 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 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 patients with cancer with COVID-19 reported an increased odds of death compared with age- and sex-matched controls (OR, 2.45;  $P < .01$ ), with a CFR of 28% [11].

Subgroups of patients with cancer 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 patients with COVID-19 in both the United States (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 patients with HM is accumulating rapidly. The largest case series include over 10 patients from the United Kingdom [26], France [24], Spain [23], and China [21] (Table 1).

An earlier study of 28 patients with HM from Wuhan, China, found that 10% were positive for COVID-19, among whom the CFR was 62% [21]. A subsequent study of 25 patients with HM 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 the general population. Of hospitalized patients, 52% developed acute respiratory distress syndrome and 33% required intubation, with a mortality of 40% at 1 month, although the authors note that elderly patients with poor prognoses were not transferred to the ICU [24]. In another study from Spain examining 34 patients with HM with COVID-19 (23% without positive polymerase chain reaction [PCR] testing), 32% of patients died. On multivariate survival analysis, active malignancy and poor Eastern Cooperative Oncology Group performance status ( $<2$ ) were independent predictors of mortality [23]. Currently, the largest study is of 35 patients with HM in the United Kingdom, of whom 69% were receiving active therapy at the time of COVID-19 diagnosis and 40% died [26].

Stem-cell transplant (SCT) recipients accounted for a small proportion of the patients with HM in existing studies. Among the larger studies of patients with HM with COVID-19, Malard et al [24] included 7 patients who had undergone SCT (5 autologous [auto-SCT], 1 allogeneic [allo-SCT], and 1 with both), of whom 86% survived, including the 2 patients with allo-SCT. The majority of patients received supportive care; 3 received lopinavir/ritonavir, anakinra, or a combination hydroxychloroquine, azithromycin, and tocilizumab. Martín-Moro et al [23] included 1 allo-SCT and 2 auto-SCT recipients, all of whom survived. In a case series of 7 SCT recipients (6 allo-SCT, 1 auto-SCT) from the United Kingdom with COVID-19, the CFR was 43%, although, notably, 1 of the 3 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 [34]. Taken together, the overall CFR among SCT recipients in the literature is 27%, potentially lower than patients with HM in general.

Among smaller case reports and series of patients with HM with COVID-29, there have been reports of patients with multiple myeloma treated with tocilizumab with favorable laboratory and clinical responses [35, 36]. Additional reports suggest that patients with Waldenström's macroglobulinemia [22] and chronic lymphocytic leukemia [31] 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 with 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 in more severe COVID-19 disease [37].

In summary, patients with cancer, and particularly those with lung cancer and HM, appear to be at higher risk of severe COVID-19 disease and mortality. A significant proportion of the patients in the literature had nosocomial acquisition, emphasizing the 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, the Netherlands, Iran, and the United States (Table 2).

Examining the larger studies including more than 10 patients each [38–56], SOT recipients with COVID-19 were predominantly male and older (median age, 51–72 years) than the overall population of patients with COVID-19 [57]. In US studies reporting race/ethnicity [41, 42, 47, 53], significant proportions of patients were Hispanic (up to 42%) [41, 42] or African American (up to 39%) [42]. 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 C-reactive protein (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 [41] and 75% in an Iran study [52], both in kidney transplant recipients. Mortality among SOT recipients ranged significantly, from 5% to 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% [42]. 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 to 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 [58–61]. In a small series of 6 patients from Italy, the 3 patients who died were over 10 years from transplant, whereas the others who had mild disease were less than 2 years post-transplant [60]. 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 [55]. In addition to the significant variability in treatment, some patients who received boosted protease inhibitors experienced significant drug–drug interactions and toxicity [62, 63]. Case series of up to 6 transplant recipients also document a favorable response among kidney transplant recipients with COVID-19 to tocilizumab [64]. While most cases of COVID-19 among SOT recipients were managed with immunosuppression reduction per the above, there were several reports describing cases where immunosuppression was maintained and patients recovered [65–67].

Of note, there have been case reports of transplant patients with HIV 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 [68]. 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 [69].

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 Antirheumatic Drugs**

Patients with various rheumatologic, dermatologic, neurologic, and gastrointestinal diseases take biologic therapies or targeted disease-modifying antirheumatic drugs (eg, 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 3 case series of COVID-19 in patients with inflammatory bowel disease (IBD), including a case series of 15 patients from Italy and France [70], 12 patients from Spain [71], and 79 patients from Italy [72]. In total, 64 of 106 patients (60%) were taking biologics (anti-tumor necrosis factor [TNF] inhibitors, vedolizumab, or ustekinumab), symptoms were typical for COVID-19, and the incidence was similar to that in the community. There were only 8 deaths, of which only 1 patient was taking a biologic. In the largest case series

**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 (%)
[38]	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)
[39]	10 kidney transplant recipients with COVID-19	China	Case series	Hospitalized (100), noninvasive ventilation (30), intubated (0)	Antivirals (100 <sup>a</sup> ), IVIG (70), steroids (80), IS reduction (80)	Recovered (80), died (10)
[40]	15 kidney transplant recipients with COVID-19	United States (NY)	Case series	Hospitalized (>80 <sup>a</sup> ), intubated (27)	Antivirals (87), tocilizumab (7), IS reduction (93)	Recovered (53), died (7)
[41]	36 kidney transplant recipients with COVID-19	China (Wuhan)	Case series	Hospitalized (78), intubated (36)	Antivirals (86), tocilizumab (7), lenrolinimumab (21), IS reduction (86)	Recovered (38), died (28)
[42]	90 SOT recipients with COVID-19 • 51% kidney, 19% lung, 14% liver, 10% heart, 6% dual	United States (NY)	Case series	Hospitalized (76), ICU (26)	Antivirals (>91 <sup>a</sup> ), tocilizumab (21), steroids (24), IS reduction (>88*)	Recovered (54), died (18)
[43]	24 liver transplant recipients with COVID-19	Italy	Survey	ICU (13)	n/a	Died (21)
[44]	13 heart transplant recipients with COVID-19	United States (MI)	Case series	Hospitalized (100), ICU (46), intubated (38)	Antivirals (62), tocilizumab (23), steroids (62)	Recovered (69), died (15)
[45]	803 heart transplant recipients, 28 with COVID-19	United States (NY)	Retrospective cohort	Hospitalized (79), intubated (28)	Antivirals (78), tocilizumab (26), steroids (47), IS reduction (83)	Recovered (69), died (25)
[46]	10 liver transplant recipients with COVID-19	Italy	Case series	n/a	Antivirals (60), steroids (30), IS reduction (70)	Died (25)
[47]	132 SOT recipients tested for COVID-19, 21 positive • 57% kidney, 14% liver, 10% lung, 19% dual	United States (TX)	Retrospective cohort	Hospitalized (67), ICU (33), intubated (24)	Antivirals (57), immunomodulatory (19), IS reduction (>86 <sup>a</sup> )	Recovered (57), died (5)
[48]	324 kidney transplant recipients ≥65 years, 16 with COVID-19	Spain	Retrospective cohort	ICU (12.5), intubated (12.5)	Antivirals (>81 <sup>a</sup> ), tocilizumab (25), steroids (38), IS reduction (100)	Recovered (50), died (50)
[49]	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)
[50]	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)
[51]	41 kidney transplant recipients with known/suspected COVID-19	United States (NY)	Case series	Hospitalized (32)	IS reduction (63)	Recovered (56)
[52]	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.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IS, immunosuppressive medication; IVIG, intravenous immunoglobulin; n/a, not available; Ref, reference; SOT, solid organ transplant.

<sup>a</sup>Accurate estimate not available from published data, minimum % listed.

[72], active IBD, age, and comorbidities were associated with worse outcomes, but the use of biologic therapies was not. An international registry recently reported 525 COVID-19 cases in patients with IBD 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 [73]. Similarly, in a national Veterans' Affairs Health System cohort study (36 COVID-19 cases out of 37 857 patients with IBD), the use of an anti-TNF

agent was not associated with an increased risk of COVID-19 infection [74].

#### **Biologics and JAK Inhibitors for Rheumatologic Disease**

There have been 6 large cross-sectional survey studies of rheumatologic patients in Italy and Spain of 162 patients [75], 320 patients [76], 458 patients [77], 530 patients [78], 959 patients [79], and 859 patients [80]. Together, these studies revealed only 25 cases of COVID-19. Twelve of the patients required hospitalization and

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

Ref	Patient Population	Geographic Location	Study Design	No. with COVID-19	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
<b>Biologics (IBD)</b>							
[70]	IBD • 80% biologics	Italy, France	Case series	15	Hospitalized (33), ICU (0)	n/a	Recovered (100)
[71]	IBD • 42% biologics	Spain	Case series	12	Hospitalized (67), ICU (8)	Antivirals (8)	Recovered (92), died (8)
[72]	IBD • 61% biologics	Italy	Case series	79	Hospitalized (28), ICU (3)	n/a	Recovered (92), died (8)
[73]	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)
[74]	IBD	United States (national)	Cohort study	36	n/a	n/a	n/a
<b>Biologics and JAK inhibitors (Rheum)</b>							
[75]	Vasculitis • 50% biologics	Italy	Cross-sectional	4	Hospitalized (50)	Antivirals (50)	Recovered (100)
[76]	Arthritis • 75% biologics, 25% JAK inhibitors	Italy	Cross-sectional	4	Hospitalized (25)	n/a	Recovered (100)
[77]	Autoimmune disease • 0% biologics	Italy	Cross-sectional	1	ICU	Antivirals, toci	Recovered
[78]	Autoimmune disease • 100% biologics	Italy	Cross-sectional	3	Hospitalized (33)	n/a	Recovered (100)
[79]	Arthritis • 100% biologics	Spain	Cross-sectional	11	Hospitalized (55), ICU (9)	n/a	Recovered (100)
[80]	Autoimmune disease • 100% biologics	Italy	Cross-sectional	2	Asymptomatic (50), hospitalized (50)	Antivirals (50)	Recovered (100)
[81]	Autoimmune • 31% biologics, 6% JAK	United States (MA)	Case-control	52	Hospitalized (44), ICU (21)	Antivirals (35), anti-IL6 (2)	Died (6)
[82]	Spondyloarthritis on anti-TNF	France	Case report	1	Hospitalized	None	Recovered
[83]	Periodic syndrome on canakinumab	Greece	Case report	1	Outpatient	None	Recovered
[84]	Systemic sclerosis on tocilizumab	Switzerland	Case report	1	Outpatient	None	Recovered
[85]	Autoimmune disease • 39% biologic or JAK	International	Case registry	600	Hospitalized (46)	n/a	Died (9%)
<b>Biologics (Derm)</b>							
[86]	Atopic dermatitis on dupilumab	Italy	Case series	2	Hospitalized (50)	Antivirals (50)	Recovered (100)
[87]	Atopic dermatitis on dupilumab	Italy	Case report	1	Asymptomatic	None	Recovered
[88]	Chronic sinusitis on dupilumab	Germany	Case report	1	Outpatient	None	Recovered
[89]	Psoriasis on ixekizumab	Italy	Case report	1	Asymptomatic	None	Recovered
[90]	Psoriasis on guselkumab	Italy	Case report	1	Outpatient	None	Recovered
[91]	Psoriasis on guselkumab or ustekinumab	Italy	Case series	2	Outpatient (50), ICU (50)	None	Recovered (100)
[92]	Psoriasis on anti-TNF or ustekinumab	United States (CA)	Case series	2	Outpatient (100)	None	Recovered (100)
[93]	Psoriasis • 100% biologics	Italy	Case series	9	Hospitalized (11), ICU (11)	n/a	Recovered (100)
<b>Biologics, JAK inhibitors (combined)</b>							
[94]	Autoimmune disease • 43% IBD, 41% rheum, 16% psoriasis • 72% biologic or JAK	United States (NY)	Case series	86	Hospitalized (16), ICU (1)	Antivirals (12), tocilizumab (1)	Recovered (99), died (1)
[95]	Patients taking biologics, tsDMARDs	Italy	Population study	9	Hospitalized (44)	n/a	Died (11)
<b>Anti-CD20 Antibodies</b>							
[96]	MS on ocrelizumab	Italy	Case report	1	Hospitalized	None	Recovered
[97]	MS on ocrelizumab	France	Case report	1	Asymptomatic	None	Recovered
[98]	MS on ocrelizumab	Iran	Case report	1	Outpatient	None	Recovered

**Table 3. Continued**

Ref	Patient Population	Geographic Location	Study Design	No. with COVID-19	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
[99]	MS on ocrelizumab	International	Case registry	74	Hospitalized (35), ICU (7)	n/a	Recovered (65), died (0), unknown (35)
[100]	GPA on rituximab	France	Case report	1	ICU	Antivirals	Recovered
[101]	SSc on rituximab	Italy	Case report	1	ICU	Tocilizumab	Died
[102]	GPA on rituximab	Switzerland	Case report	1	Hospitalized	None	Recovered
[103]	MS • 50% ocrelizumab, 50% rituximab	Spain	Case series	4	Hospitalized (25)	n/a	Recovered (100)

Abbreviations: Abs, antibodies; COVID-19, coronavirus disease 2019; Derm, dermatologic condition; GPA, granulomatosis with polyangiitis; IBD, inflammatory bowel disease; ICU, intensive care unit; IL, interleukin; JAK, Janus kinase; MS, multiple sclerosis; n/a, not available; Ref, reference; Rheum, rheumatologic disease; SSc, systemic sclerosis; TNF, tumor necrosis factor; toci, tocilizumab; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

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 [77]. Similarly, a case-control study from Boston compared 52 patients with COVID-19 with rheumatologic disease (31% on biologics, 6% JAK inhibitors) with 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 [81]. There are also case reports of mild COVID-19 in patients taking an anti-TNF [82] and inhibitors of interleukin (IL) 1 [83] and IL-6 [84].

The Global Rheumatology Alliance recently released its report of 600 patients with COVID-19 with underlying rheumatologic disease (39% taking biologics or JAK inhibitors) [85] of whom 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 [86, 87] or chronic sinusitis [88]. In patients with psoriasis, there are several case reports of mild COVID-19 in patients taking ixekizumab (IL-17 inhibitor) [89], guselkumab (IL-23 inhibitor) [90], or ustekinumab (IL-12/IL-23 inhibitor) [91, 92]. Similarly, there is a case series of COVID-19 in 9 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 [93]. There is also a report of a patient taking guselkumab for psoriasis who developed severe disease but recovered [91].

#### 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 COVID-19 was recently published [94]. Seventy-two percent of patients were on a biologic or JAK inhibitor, but the 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-19 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 of hospitalization and death than those in the general population [95].

#### Anti-CD20 Antibodies

There are 5 reported cases of asymptomatic to mild infection in patients with multiple sclerosis taking ocrelizumab [96–98,103]. In addition, a case registry drawn from a pharmaceutical global safety database identified 74 confirmed COVID-19 cases in patients with multiple sclerosis (MS) taking ocrelizumab: 35% required hospitalization, 7% required ICU care, and there were no deaths (although 35% had unknown outcomes). The data are more mixed with rituximab, however. There are 3 reported cases of mild disease in patients taking rituximab for granulomatosis with polyangiitis (GPA) [102] or MS [103], but there are also reports of severe (but recovered) infection in a patient with GPA [100] as well as a fatal case in a patient taking rituximab for systemic sclerosis [101].

In summary, the existing data do not show an increased risk of severe COVID-19 in patients taking biologic therapies or targeted disease-modifying antirheumatic 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 7 patients with primary immunodeficiency and COVID-19 (2 with agammaglobulinemia, 5 with common variable immune deficiency [CVID]) [104].

**Table 4. Summary of Studies of COVID-19 in Patients With Primary Immunodeficiency**

Ref	Patient Population	Geographic Location	Study Design	No. With COVID-19	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
[104]	XLA, ARA, CVID	Italy	Case series	7	Asymptomatic (14), hospitalized (86), ICU (43)	Antivirals (100), tocilizumab (43), IVIG (100)	Recovered (86), died (14)
[105]	CVID	United States (OH)	Case report	1	ICU	IVIG	Recovered

Abbreviations: ARA, autosomal recessive agammaglobulinemia; COVID-19, coronavirus disease 2019; CVID, common variable immunodeficiency; ICU, intensive care unit; IVIG, intravenous immunoglobulin; Ref, reference; XLA, X-linked agammaglobulinemia.

This series reported that the patients with CVID had a more severe course (3 requiring ICU admission and 1 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 [105] (Table 4).

#### Human Immunodeficiency Virus

In addition to immunosuppression, people living with HIV (PWH) might be at risk of 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 older than 50 years and many have comorbidities such as diabetes, hypertension, and cardiovascular disease [106]. On the other hand, HIV might be protective against severe COVID-19 as immunosuppression could help temper 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 [107]. Although there was hope that some of the protease inhibitors might have activity against SARS-CoV-2, existing data do not support the efficacy of lopinavir/ritonavir [108] or darunavir [109].

There have been multiple case series from around the world describing the course of COVID-19 disease in PWH [110–121] (Table 5). The majority of these cases were in patients with

**Table 5. Summary of Studies of COVID-19 in Patients With Human Immunodeficiency Virus**

Ref	Patient Population	Geographic Location	Study Design	No. With COVID-19	Clinical Severity (%)	COVID-19 Treatment (%)	Outcomes (%)
[110]	HIV, median CD4 592	Italy	Case series	3	Hospitalized (100), ICU (33)	Antivirals (100), tocilizumab (33)	Recovered (100)
[111]	HIV, CD4 >200 in 80%, median CD4 604	Spain	Case series	5	Hospitalized (100), ICU (40)	Antivirals (80), IFN (40)	Recovered (80)
[114]	HIV, CD4 >200 in 75%, median CD4 422	Turkey	Case series	4	Hospitalized (100), ICU (25)	Antivirals (75)	Recovered (75), died (25)
[115]	HIV, CD4 >200 in 97%, mean CD4 636	Italy	Case series	47	Hospitalized (28), ICU (4)	Antivirals (30), tocilizumab (4)	Recovered (96), died (4)
[116]	HIV, median CD4 395	United Kingdom	Case series	18	Hospitalized (100), ICU (28)	Antivirals (22)	Recovered (67), died (28)
[117]	HIV, CD4 >200 in 78%, median CD4 504	United States (NY)	Case series	9	Hospitalized (100), ICU (56)	Antivirals (44)	Recovered (22), died (78)
[118]	HIV, CD4 >200 in 100%, median CD4 305	United States (IL)	Case series	5	Hospitalized (100), ICU (20)	Antivirals (40)	Recovered (100)
[119]	HIV, CD4 >200 in 94%, median CD4 670	Germany	Case series	33	Hospitalized (42), ICU (18)	n/a	Recovered (91), died (9)
[120]	HIV, CD4 >200 in 80%, mean CD4 396	United States (NY)	Case series	31	Hospitalized (100), ICU (23)	Antivirals (77), steroids (26), tocilizumab (7)	Recovered (68), died (26)
[121]	HIV, CD4 >200 in 100%, median CD4 1068	United States (NY)	Case series	4	Hospitalized (25)	None	Recovered (100)
[112]	HIV, Median CD4 551	United States (NJ)	Case series	27	Hospitalized (49), ICU (11)	Antivirals (26), steroids (4)	Recovered (93), died (7)
[113]	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)

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; ICU, intensive care unit; IFN, interferon; n/a, not available; Ref, reference.



well-controlled HIV; 75–100% of patients in these studies had a CD4 greater than 200 cells/ $\mu$ L and the median CD4 count ranged from 305 to 1068 cells/ $\mu$ L. In terms of disease severity, 25–100% 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 [117].

In the largest case series from Spain of 51 patients with HIV with COVID-19, the clinical, laboratory, and radiologic parameters of COVID-19 in PWH were similar to those seen in the general population [113]. 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.

## CONCLUSIONS

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 of more severe COVID-19 disease. Third, patients taking biologics may not be at higher risk of 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 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 healthcare disparities, access to healthcare resources, and therapeutics in determining outcomes in different immunocompromised patient populations.

## Note

**Potential conflicts of interest.** The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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