COVID-19 in Patients with Hematologic Malignancies: Clinical Manifestations, Persistence, and Immune Response

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Keywords

Hematologic malignancies · Novel coronavirus disease · Immune pathophysiology · Viral shedding

Abstract

Background: The clinical presentation of coronavirus disease 19 (COVID-19) is the result of intricate interactions between the novel coronavirus and the immune system. In patients with hematologic malignancies (HM), these interactions dramatically change the clinical course and outcomes of COVID-19. **Summary:** Patients with HM and COVID-19 are at an increased risk for prolonged viral shedding, more protracted and severe presentation, and death, even when compared to other immunocompromised hosts. HM (e.g., multiple myeloma, chronic lymphocytic leukemia) and anticancer treatments (e.g., anti-CD20 agents) that impair humoral immunity markedly increase the risk of severe COVID-19 as well as protracted viral shedding and possibly longer infectivity. Cytokine release syndrome (CRS) is an important player in the pathophysiology of severe and fatal COVID-19. Treatments targeting specific cytokines involved in CRS such as interleukin-6 and Janus kinase have

proven beneficial in COVID-19 patients but were not assessed specifically in HM patients. Although neutropenia (as well as neutrophilia) was associated with increased COVID-19 mortality, granulocyte colony-stimulating factors were not beneficial in patients with COVID-19 and may have been associated with worse outcomes. Decreased levels of T lymphocytes and especially decreased CD4+ counts, and depletion of CD8+ lymphocytes, are a hallmark of severe COVID-19, and even more so among patients with HM, underlying the important role of T-helper dysfunction in severe COVID-19. In HM patients with intact cellular immunity, robust T-cell responses may compensate for an impaired humoral immune system. Further prospective studies are needed to evaluate the mechanisms of severe COVID-19 among patients with HM and assess the efficacy of new immunomodulating COVID-19 treatments in this population. **Key Messages:** Understanding the immunopathology of COVID-19 has greatly benefited from the previous research in patients with HM. So far, no COVID-19 treatments were properly evaluated in patients with HM. Patients with HM should be included in future RCTs assessing treatments for COVID-19.

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Introduction

Patients with hematologic malignancies (HM) exhibit various immune deficiencies resulting from either the disease or its treatment [1, 2]. Naturally, the emergence of the coronavirus disease 2019 (COVID-19) was particularly concerning in this population [3]. The extremely high mortality of HM patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was evident early in the pandemic [4, 5]. Many physicians recommended strict sequestration and suggested postponing the initiation of HM treatments, in an attempt to minimize the resultant immune dysfunction during the pandemic [6]. While the persistence of the pandemic gradually made this approach impractical, it was the understanding of the interplay between different immune functions and COVID-19 that opened the possibilities of treating HM in the COVID-19 era [7, 8]. Thus, understanding the immunopathology of COVID-19 resulted in better care for HM during the pandemic, even without coinfection with COVID-19 [9].

The clinical presentation of COVID-19 is the result of intricate interactions between SARS-CoV-2 and the immune system [10, 11]. This elaborate web is elucidated by the study of the unique characteristics of COVID-19 in HM patients, an invaluable tool researching this neoteric disease [12]. Understanding the immune pathophysiology behind severe or critical COVID-19 can in turn guide the treatment and the development of novel therapeutics addressing specific HM. In this review, we aim to help clarify what is known of the unique clinical characteristics and immunology of COVID-19 in patients with HM, in the hope that a succinct summary of the available evidence will not only help tailor the best treatment to HM patients infected with COVID-19 but also improve our understanding of the underlying pathophysiology of COVID-19 in general.

Methods

This manuscript is a narrative review. The following databases were searched for publications available through November 15, 2021: PubMed, WHO COVID-19 repository, and Google Scholar. Search terms included: "hemato* or heamato*," "COVID-19 or SARS-CoV-2," "shedding," "treatment or therapy*," "il-1 or interleukin-1," "il-6 or interleukin-6," "JAK*," "TNF*," "humoral immunity," "vaccin*," "cellular immunity," "anti-CD20," "T-helper or CD4," "Burton's tyrosine kinase or BTK." Additional studies were identified through review of reference lists of included studies. All authors participated in study identification, screening, and data extraction; all included studies were reviewed by at least 2 authors. Studies reporting exclusively on pediatric patients were excluded.

Results and Discussion

Clinical Manifestation and Disease Course

HM are a risk factor for more severe and prolonged COVID-19, and patients tend to fare worse even than patients with solid malignancies (SM) or patients treated with immunomodulatory medications for nonmalignant diseases. A recent retrospective analysis examined the clinical presentation and outcome of 98,951 patients with COVID-19 in Catalonia, Spain [13]. Patients with HM were not only twice as likely to present with severe COVID-19 requiring hospitalization (hazard ratio [HR] 2.51, 95% CI [2.12–2.98]) compared to the general population, but also when comparing with patients with SM (HR 1.32, 95% CI [1.21–1.44]). These differences were even more pronounced when looking only at patients with newly diagnosed (<1 year) HM (HR 6.18 [4.31–8.86] than the general population and 2.24 [1.34–3.76] than patients with SM). The increased risk of patients with HM to have severe COVID-19 at presentation, to have a longer duration of hospital admission, and be more likely to die is consistent in reported studies across the globe when compared to all patients [14–16], patients with SM [13, 17], and patients treated with immunosuppressive medications [18]. In a large survey performed by the Scientific Working Group Infection in Hematology of the European Hematology Association, including 3,801 HM patients with COVID-19, 64% of patients developed severe or critical disease, 18% were admitted to an intensive care unit, and 31% died [6]. Compared to the general population, HM patients were more likely to suffer from COVID-19 symptoms including fever (63%), cough (55%), sore throat (7%), diarrhea (10%), and dyspnea (40.5%) and to be hospitalized (61%) [14]. A prospective study in Italy followed 536 COVID-19 patients with HM [3]. In a multivariate cox regression, the following types of HM were shown to bear the greatest risk for death from COVID-19: acute myeloid leukemia (3.49, 1.56–7.81), multiple myeloma (2.48, 1.31–4.69), and non-Hodgkin's lymphoma (2.19, 1.07–4.48). Data reported in other studies [6, 14–16, 19] were similar. Interestingly, while age, HM severity, and shorter time from HM diagnosis were strongly associated with increased mortality, other comorbidities and time interval between last HM treatment and COVID-19 infection were not [6]. These observations point toward a more significant immunomodulatory effect of HM themselves, rather than the effects of treatments for HM, as the main factors influencing mortality and morbidity in HM patients with COVID-19.

Beyond increased mortality, COVID-19 in patients with HM has several outstanding clinical characteristics.

Disease course tends to be more prolonged. While time from infection to symptom onset seems to be similar to the general population, time from symptom onset to maximal required O₂ supplementation is significantly longer (HR 1.48, 95% CI [1.04–1.92]) [20]. Interestingly, while thrombocytopenia seems to be much more prevalent in HM patients with COVID-19 [7], we found no reported evidence of an increased risk of disseminated intravascular coagulopathy or superinfection in this population compared to HM unaffected by COVID-19 [6, 14–16, 18–21]. Conversely, some reports show increased venous thromboembolism in HM, although whether COVID-19 actually increases venous thromboembolism risk among patients with HM, already at an increased risk due to their malignancy, is unknown [22].

Data detailing the clinical characteristics of COVID-19 in specific HM are limited. Table 1 summarizes the available data of clinical manifestations by HM type. Within HM patients, those with acute myeloid leukemia and myelodysplastic syndrome are repeatedly shown to suffer from more severe disease, protracted clinical courses, and high rates of ICU admissions [23, 24]. The reported rates of severe COVID-19 in this group are around 40% in different studies with mortality occurring in up to 35–54% of cases [23–26]. Acute lymphoblastic leukemia was also associated with high rates of symptomatic disease (75%), oxygen support (38%), ICU admission (21%), and mortality (33%) [27]. Patients with HM types commonly associated with hypogammaglobulinemia including chronic lymphoblastic leukemia, non-Hodgkin lymphoma, and multiple myeloma had high rates of hospital (74–89%) and ICU admissions (20–27%), disease severity (60–70%), and mortality (23–30%) [3, 6, 28–32]. aCD20 treatment, often used to treat some of these HM types, may further add to the protracted disease course [33, 34]. aCD20 was associated with severe disease and worse survival in some reports [33, 35] but not in others [15, 36]. In a study including 856 lymphoma patients (mostly non-Hodgkin lymphoma), 55% were hospitalized and 37% had severe or critical disease with a case fatality rate of 19.5%. In this study, aCD20 treatment was not associated with worse outcome [15]. Notably, Hodgkin lymphoma patients had relatively favorable COVID-19 courses and outcomes [3, 6]. Myeloproliferative diseases were associated with COVID-19 severity and higher mortality depending on the type of disease with mortality reaching 48% in patients with myelofibrosis [6, 37]. Last, COVID-19 was associated with severe disease and protracted courses in recipients of chimeric antigen receptor T cell (CAR T cell) or hematopoietic stem cell transplant (HCT),

especially in the first 12 months following the procedure with moderate to severe disease reported in 50–74% and mortality in 16–22% [38–40].

Persistence

A plethora of clinical and epidemiological evidence indicates that HM patients infected with COVID-19 have protracted viral shedding and possibly longer infectivity [20]. Technical limitations and safety concerns make viral cultures impractical in assessing viral shedding in most settings. A widely accepted alternative is polymerase chain reaction (PCR) cycle threshold (Ct) indirectly reflecting the viral burden [41]. Ct has been repeatedly shown to correlate well with both culture positivity [42] and infectivity [43]. Patients with HM bear the highest risk of protracted shedding, as evidenced by nasal swabs with Ct >30. In one study, PCR remained positive for a mean of 21.2 days (SD 15.9) in HM patients compared to 7.4 (SD 5.6) in matched controls without HM [20]. One retrospective study [44] compared 70 patients with SM with 35 HM patients. HM took almost twice as long to reach Ct >30 (HR 1.71, 95% CI [1.004–2.9]) or negativity (HR 2.34 [1.1–5.1]). Interestingly, the maximal viral load in nasopharyngeal swabs, shown to correlate with disease severity and survival [45], was not elevated in patients with HM compared with patients with SM or immunocompetent hosts [21, 42].

Serological studies indicate a similar pattern, with nasopharyngeal shedding and seroconversion both taking twice as long in HM patients (HR 1.97, 95% CI [1.56–2.38]) [46]. These differences seem to be larger among patients treated with anti-CD20, CAR T cell, or HCT recipients [33, 47].

Prolonged shedding amplifies the dilemma of release from isolation. No universally accepted guidelines were developed for severely immunocompromised patients with COVID-19, and many infection control services require two consecutive negative nasopharyngeal swabs before immunocompromised patients are allowed to stop isolation. While some case reports have raised concerns about viable viruses shed by patients with HM after the Ct surpassed 30, these might represent reinfection [48, 49]. Current literature and a limited prospective study by Mowrer et al. [50] suggest that releasing from isolation HM patients with nasopharyngeal swab Ct > 30 is safe [42, 47, 50].

Immunology and Pathogenesis

Different HM and treatment modalities are associated with unique patterns of immune impairment. Moreover,

Table 1. Immune pathophysiology and clinical presentation of COVID-19 by the type of HM

Type of HM	Mechanism of impaired immunity	Clinical presentation of COVID-19	COVID-19 persistence	References
Acute myeloid leukemia MDS	Myelosuppression and severe prolonged neutropenia secondary to underlying disease and its treatment In MDS impaired neutrophil and T-cell function and baseline elevated IL-1, IL-6, TNF, and other cytokines. Immune impairment associated with older age	More severe disease Higher risk of mortality Prolonged LOS	Prolonged viral shedding	[3, 4, 6, 23–26, 137]
Acute lymphoblastic leukemia	Myelosuppression secondary to underlying disease and treatment Hypogammaglobulinemia Treatment-related B-cell dysfunction	Higher risk of mortality		[6, 27]
CLL	Hypogammaglobulinemia, B- and T-cell defects, CD4+ lymphopenia, innate immune dysfunction, and neutropenia	More severe disease and hospitalization Higher risk of mortality Possibly better outcomes with BTK inhibitors	Prolonged viral shedding Lack of seroconversion	[6, 28–31, 123]
Lymphoma	Hypogammaglobulinemia, neutropenia, and lymphopenia Treatment causing cellular and humoral immune deficiency	Higher risk of mortality in NHL and in patients with relapsed/refractory disease Prolonged LOS Outcome better for Hodgkin lymphoma	Lack of seroconversion	[3, 6, 19, 33, 138]
Anti-CD20 treatments	Depleted circulating B cells and significantly impaired IgG and IgM responses	Prolonged LOS Probably associated with increased mortality and disease severity	Prolonged viral shedding Lack of seroconversion	[33–36, 61]
Multiple myeloma	B-cell dysfunction leading to hypogammaglobulinemia, T-cell, dendritic cell, and NK cell abnormalities	Higher risk of mortality Elevation of inflammatory markers and severe hypogammaglobulinemia associated with higher mortality	Prolonged viral shedding median time to negative PCR 43 days Lack of seroconversion	[6, 32, 139]
Chronic myeloid leukemia		Relatively lower mortality compared to other HM		[23, 118]
Myeloproliferative neoplasms		Higher mortality (mainly PMF) Possible protective effect of JAK inhibitors High risk for VTE (mainly ET)		[3, 22, 37]
HCT	Neutropenia (pre-engraftment period) Impaired humoral and cellular immunity with prolonged reconstitution immune suppression (allogeneic > autologous HCT)	More moderate to severe COVID-19 Higher mortality Mortality higher when COVID-19 occurs within 12 months of transplantation	Prolonged viral shedding (median time to negative PCR 7.7 weeks) Lack of seroconversion	[3, 38–40, 133]
CAR T-cell therapy	High risk of CRS, long-term B-cell depletion, hypogammaglobulinemia, and cytopenia	Increased risk of moderate-severe COVID-19 pneumonia and higher mortality	Prolonged viral shedding Lack of seroconversion	[1, 39, 40, 140]

MDS, myelodysplastic syndrome; TNF, tumor necrosis factor; BTK, Bruton tyrosine kinase; NHL, non-Hodgkin lymphoma; LOS, length of stay; NK, natural killer cells; PCR, polymerase chain reaction; HM, hematologic malignancy; PMF, primary myelofibrosis; JAK, Janus kinase; VTE, venous thromboembolism; ET, essential thrombocythosis; HCT, hematopoietic cell transplantation; CRS, cytokine release syndrome.

COVID-19 infection itself has significant effects on the immune system [10, 12, 51]. Immune activation by the virus acts as a double-edged sword with both over- and underactivated immune response potentially causing worse outcomes. Severe COVID-19 infection has been linked to immune dysregulation involving nearly all of the immune system components, including impaired interferon production, lymphopenia, paradoxical increase in proinflammatory cytokines, increases in effector and activated CD4 and CD8 T cells, and robust plasmablast differentiation [9, 11, 52–54].

The complex interactions between the HM, COVID-19, and the immune system likely underline the severity and dismal outcomes of COVID-19 in these patients. Table 1 summarizes the evidence existing on the manifestations of COVID-19 according to the specific types of HM. In the next sections, we discuss the accumulated evidence on the interactions between COVID-19 and the specific components of the immune system.

Innate Immune System

The innate immune system serves as the frontline response for viral infections including COVID-19 and regulates immune response [51]. In the following sections, we will focus on the innate immune system components most relevant to patients with HM.

Cytokine Response

When examining the natural progression of very severe or ultimately fatal COVID-19, a biphasic pattern is evident. A mainly viral phase is gradually replaced by a systemic inflammatory response syndrome. This phase is frequently characterized by disordered coagulation-fibrinolysis and marked by extremely high levels of D-dimer, in addition to rising white blood cell counts and rise in markers of inflammation, and may lead to multiple organ failure. This common pathway has been described in multiple other clinical scenarios including rheumatological (i.e., rheumatoid arthritis or systemic lupus erythematosus), infectious (particularly Gram negative bacteria), and hematologic (allogeneic HCT [allo-HCT], CAR T-cell therapy) conditions. A massive release of proinflammatory cytokines and chemokines, often referred to as cytokine release syndrome (CRS), was first recognized following allo-HCT over two decades ago and has been shown to be central in this pathway [55].

The exact pathophysiological cascade leading to CRS remains elusive and likely involves multiple dysregulated factors in both the innate and adaptive immune systems. However, strong *in vivo* evidence points toward the dam-

age-associated molecular patterns-induced activation of the innate immune system [56]. Macrophages undergoing pyroptosis release interleukin-1 (IL-1) and the activation of the NF κ B and JAK-STAT cascades [57]. Mitochondrial damage resulting in the release of mitochondrial DNA and cardiolipin promotes the release of interferon- γ and other proinflammatory cytokines, including interleukin-6 (IL-6), activating the endothelium and promoting coagulation-fibrinolysis, ultimately resulting in diffuse intravascular coagulopathy [58]. This explains, at least in part, the massive rise in D-dimer and other markers of coagulation-fibrinolysis in COVID-19, and the correlation between these markers and disease severity and mortality [3, 13, 14, 59]. Tumor necrosis factor (TNF), released by monocytes and somatic cells (induced by rising levels of IL-18 and IL-6) [60], triggers apoptosis throughout various tissues, as evidenced by rising levels of lactate dehydrogenase and aspartate aminotransferase. TNF is the major inducer of ferritin release from the reticuloendothelial system, and levels of serum ferritin are thus strongly correlated with COVID-19 severity [38, 54]. Interestingly, all of the abovementioned markers are significantly elevated in patients with HM infected with COVID-19 [60, 61]. The understanding of the importance of CRS in the pathophysiology of severe and fatal COVID-19 led the quest of finding therapeutics targeting this common pathway, many of which were first developed in the context of allo-HCT and CAR T-cell therapy [39].

The recombinant IL-1 receptor antagonist anakinra was suggested as a potential treatment early in the pandemic, backed by the observation that patients with severe COVID-19, and particularly HM patients infected with COVID-19, had increased levels of IL-1 [55, 58, 59, 62]. Some meta-analyses found anakinra to decrease mortality when compared with placebo (adjusted RR 0.32, 95% CI [0.20–0.51]) [63]. However, further revision of available data [64] showed no added benefit to anti-IL-1 agents when compared to standard care that includes dexamethasone or other glucocorticoids [65, 66]. Limited clinical data regarding canakinumab [67] and rilonacept [65, 66] show similar, and disappointing, results. While no RCTs evaluated patients with HM specifically, anecdotal evidence supports the lack of added efficacy of anakinra to standard COVID-19 therapy in patients with HM [68, 69].

The Janus kinases inhibitor (JAKi) of subtypes 1 and 2, baricitinib, was shown to significantly reduce mortality, particularly in severe COVID-19 [70]. Mortality at day 28 post hospitalization was significantly lower (pooled

RR 0.57, 95% CI [0.41–0.78]) for all patients on standard care [66, 70, 71]. This benefit was even more pronounced when only patients on high-flow oxygen support were included (pooled RR 0.42, 95% CI [0.30, 0.59]) [72].

Interestingly, the use of JAKi in HM was probably an important catalyst in the interest JAKi sparked as a potential treatment for COVID-19. Early anecdotal reports suggested that HM patients with COVID-19 treated with either ruxolitinib or tyrosine kinase inhibitors (mostly in patients with CML) [73] were less likely to have severe COVID-19 [74]. While no studies specifically excluded patients with underlying HM, in two of the largest studies, patients presenting with neutropenia (ANC <1,000/ μ L) were excluded [70, 71]. Regretfully, this interest is yet to translate into specific clinical trials evaluating JAKi in HM patients infected with SARS-CoV-2, with or without neutropenia. Bearing in mind this important limitation, JAKi were consistently shown to be the safest of all immunomodulators for COVID-19 [66, 70–72]. Tofacitinib seems to have similar efficacy and safety, but data supporting its use are less robust [66, 72].

Of the four IL-6 inhibitors developed, tocilizumab, a humanized monoclonal antibody targeting the IL-6 receptor, is the most studied in COVID-19. Some well-designed prospective RCTs and meta-analyses have shown tocilizumab alone and tocilizumab with dexamethasone to improve survival at 28 days post hospitalization (pooled RR 0.89, 95% CI [0.82–0.97]). Thus, most guidelines [75–77] recommend the addition of tocilizumab to dexamethasone and standard care in patients on high-flow oxygen support. Treating HM patients infected with COVID-19 makes sense, since IL-6 levels are particularly high in HM patients infected with COVID-19 [55, 78], and tocilizumab has been successfully implemented in the treatment of CRS in HM in the past, particularly in the context of CAR T-cell therapy [79]. However, all nine published clinical trials [80–86] excluded patients with absolute neutrophil count below 1,000 cells/ μ L and some explicitly excluded patient with active HM [80–86]. While current guidelines [77], based on published evidence, do recommend the addition of tocilizumab to standard care in HM patients without neutropenia, a clinical trial is currently conducted to assess the effects of tocilizumab in this population [87].

TNF inhibitors (TNFi) were also suggested as potential therapies for COVID-19 [88]. This was mainly based on the observation that patients on TNFi tended to be hospitalized less and had overall better prognosis [89] than other patients with rheumatological or other autoimmune-inflammatory diseases [90]. However, a small random-

ized trial involving 68 patients found no added benefit of adalimumab, an anti-TNF- α antibody, compared to standard care including dexamethasone and remdesivir, in terms of clinical course, length of hospital stay, and rates of mechanical ventilation or mortality [91]. We found no evidence specifically applicable to patients with HM.

Neutrophils

Patients with HM frequently experience neutropenia as a side effect of their anticancer therapy and occasionally secondary to the underlying disease itself. While neutropenia is associated with increased risk and severity of various infections, its effect on COVID-19 outcomes is not well understood. Both low and high neutrophil counts have been linked to higher mortality in COVID-19 [54, 92]. In a multicenter study from Spain including HM patients, neutropenia of less than 500 cells/ μ L was an independent risk factor for mortality [38]. Similarly, neutropenia was associated with worse outcomes in a cohort of HCT and CAR T-cell therapy recipients with COVID-19 [40], albeit other studies in various HM patients failed to demonstrate a similar association [93]. On the other hand, a high neutrophil count was also shown to be a risk factor for disease progression, ARDS, and mortality in COVID-19-infected patients [93, 94]. In a meta-analysis, neutrophilia at COVID-19 presentation was associated with an 8-fold increased odds of severe disease and mortality [95]. Furthermore, the neutrophil-to-lymphocyte ratio was identified as an independent risk factor for critical illness in patients with COVID-19 infection [11, 96]. Neutrophils were shown to mediate pulmonary damage in COVID-19 via rapid infiltration into the lungs, production of neutrophil extracellular traps, and overproduction of different chemokines and cytokines that eventually lead to a cytokine storm, lung injury, and ARDS [97, 98]. Neutrophil extravasation was also demonstrated in the alveolar spaces of lungs in autopsies of patients succumbing to COVID-19 [97]. Consequently, a concern was raised toward the use of granulocyte-promoting medications such as recombinant human granulocyte colony-stimulating factor (rhG-CSF, filgrastim) in COVID-19-infected individuals.

Early in the pandemic, G-CSF and rhG-CSF were proposed as potential treatments for patients with COVID-19-induced lymphopenia and no cancer [99, 100] as well as in cancer patients with COVID-19 at high risk for febrile neutropenia [101]. In a randomized clinical trial in lymphopenic patients with COVID-19 and no cancer, rhG-CSF treatment did not increase clinical improvement but may have reduced the number of patients de-

veloping critical illness or death [99]. Recently, evidence has accumulated as to the harmful potential of these growth factors in the setting of COVID-19 [102, 103]. A case series from Memorial Sloan Kettering Cancer Center described three COVID-19 patients who received G-CSF and developed clinical and respiratory deterioration within 72 h [104]. A subsequent observational study in 379 patients demonstrated that outpatient receipt of G-CSF led to a higher number of hospitalizations, need for high levels of oxygen supplementation, and death. This effect was predominantly seen in patients that exhibited a high response to G-CSF based on the increase of absolute neutrophil counts post-G-CSF administration [105]. G-CSF administration was also associated with a substantial increase in the neutrophil-to-lymphocyte ratio, which, as noted above, is an independent risk factor for mortality in hospitalized patients with COVID-19 [105]. More studies are needed to define the specific indications for G-CSF administration in neutropenic patients with COVID-19. In clinical practice, the risks and benefits should be weighed, and overall, G-CSF should be avoided when no strong indication exists and considered carefully in patients with COVID-19 and severe neutropenia at high risk for other infectious complications.

Natural Killer Cells

Antibody-coated cells infected with SARS-CoV-2 interact with killer-cell immunoglobulin-like receptors, leading to natural killer (NK)-induced lysis of infected cells. NK cell absolute count and percentage of all lymphocytes are well correlated with time to negative nasopharyngeal swab PCR [106] and reversely correlated with the severity of COVID-19 symptoms [107, 108]. This seems particularly relevant to patients with HM. NK cell counts were significantly lower in these patients, even when adjusted for COVID-19 severity [109, 110].

Adaptive Immune System Humoral Immune Response

The humoral immune system is responsible for the production of neutralizing antibodies and has an essential protective role in controlling infection at later disease stages and preventing future reinfections. For most acute viral infections, neutralizing antibodies rapidly rise after infection due to a burst of short-lived antibodies secreting cells and then decline before reaching a stable plateau that can be maintained for years to decades by long-lived plasma and memory B cells [111]. The critical importance of humoral immunity in the pathogenesis and prognosis of COVID-19 is evident on multiple facets.

First, COVID-19 affects the humoral immune system in previously healthy hosts. Lymphopenia was noted to correlate with worse prognosis and to be the most prevalent hematologic abnormality in COVID-19 patients early in the pandemic, affecting over 85% of severe cases [62]. Looking at lymphocyte subtypes, B cells are mostly reduced in patients with severe or critical COVID-19 [112, 113]. Further underlying the importance of humoral immunity in COVID-19, B-cell subsets mostly linked to antibody production tend to increase in mild and moderate COVID-19, especially as the disease progresses toward resolution, and to decrease in critical and severe COVID-19. Transitional B cells [114], as well as memory B cells [115], all exhibit these trends, with levels strongly correlated with decreased survival. Conversely, massive overactivation of B cells can herald worse outcomes [61], similar to the U-shaped correlation of disease severity and levels of neutrophils [92].

Impaired humoral immunity is a common characteristic in many hematologic cancers, as either part of HM natural pathophysiology or a result of specific treatments. HM patients with COVID-19 were shown to have lower lymphocyte counts than controls, even when corrected for disease severity [116]. In a small study, HM showed significantly lower B-cell (but not T-cell) counts compared with non-HM patients of similar COVID severity [8].

Second, there is mounting evidence supporting the utmost importance of effective humoral response for viral clearance. This has been the accepted explanation of the observation that patients with HM in which humoral immunity is most impaired, i.e., chronic lymphocytic leukemia (CLL) and multiple myeloma, bear an exceptionally poor prognosis when infected with SARS-CoV-2 [16, 117, 118]. A cohort of 31 patients with severely impaired B-cell function (mainly due to prior anti-B-cell therapy and X-linked agammaglobulinemia) had much longer clinical courses and viral shedding, as well as increased propensity of recurrent COVID-19 [119]. Prolonged viral shedding was noted, in correlation with decreased or absent COVID-19-specific antibodies, in patients with HM, and specifically in patients with CLL and multiple myeloma patients treated with anti-CD20 agents [117]. In another study, 9/21 (43%) patients with HM and only 10/97 (10%) SM patients did not seroconvert over 60 days from the initial COVID-19 diagnosis ($p = 0.0012$), and among those who did seroconvert, antibody titers were significantly lower in the HM group [60]. Similarly, in a cohort from the USA, HM patients, despite receiving convalescent plasma, had significantly lower COVID-

19-specific antibodies than SM patients [61]. This is despite some evidence of possible antibody production by noncirculating cells, as reported in some patients with deep lymphopenia who lacked any circulating B cells [40].

Third, patients receiving anti-CD20 therapy (aCD20), i.e., obinutuzumab or rituximab, are at increased risk for COVID-19 mortality, prolonged infection, protracted viral shedding, and decreased protection as a result of vaccination [61]. While increased mortality was not evident in all cohorts [36], other [35, 120], well-designed (albeit retrospective) studies showed increased mortality risk (HR 2.16, 95% CI [1.03–4.54]) [120]. Perhaps more importantly, aCD20 deeply impairs the immune response to COVID-19 vaccination. One study of over 4,000 patients on immunomodulatory medications in the Netherlands found aCD20 to have the greatest impact on vaccination-induced seroconversion [121]. Not unlike other viral vaccines (e.g., influenza), aCD20 practically eliminates the immunogenicity of vaccines for at least 3 months, and as long as 12 months after the last aCD20 dose [122].

Of note, Bruton tyrosine kinase inhibitors (BTKi) such as ibrutinib may have some protective effects against COVID-19. One observational study of 190 patients with CLL found CLL patients treated with ibrutinib to be less likely to be hospitalized or have severe COVID-19 (OR 0.44, 95% CI [0.20–0.96] compared patients treated with any other CLL-specific treatment [28]. Findings were similar in later studies [123, 124]. This observation may be related to that fact that BTKi, commonly thought of as anti-B-cell medications, have a myriad of other immunomodulatory effects, particularly in reducing proinflammatory cytokines and affecting other components of innate immunity, such as macrophages [125]. A randomized controlled trial showed the addition of ibrutinib to significantly inhibit the release of CRS-associated cytokines, including the abovementioned IL-6, TNF, and IL-1 [126]. Observational studies in humans and substantial *in vitro* evidence point toward the potential of BTKi to reduce CRS and modulate macrophage differentiation [127].

Cellular Adaptive Response

T cells have a crucial role in the regulation of immune responses, including mediating antibody production by B cells, antigen-specific cell-mediated immunity important in the elimination of intracellular infections (mainly CD4+ T cells), as well as conferring cytotoxic activity against infected cells (mainly CD8+ T cells). Emerging data suggest that T-cell responses to COVID-19 are long

lived and important for the protection against reinfection, possibly well beyond the period of seropositivity [128]. Hence, T-cell dysfunction secondary to HM and potentially aggravated by the virus itself may affect COVID-19 course and outcomes.

Vast evidence exists as to the effect of COVID-19 itself on T-cell counts and function. Patients with COVID-19 were shown to have decreased counts of all T-cell subsets with a relatively modest decrease in CD4+ T cells and a more pronounced decrease in CD8+ T cells resulting in an elevated CD4/CD8 ratio. Low T-cell subset counts were related to the severity and prognosis of COVID-19 [55, 112, 129–131]. Interestingly, the counts of all T-cell subsets dramatically recovered in most patients who managed to eliminate the virus (namely, had a negative repeated COVID-19 PCR), but showed no such recovery in patients with persistently positive PCR [112, 129].

Low CD4+ T-cell counts were independently strongly correlated with COVID-19 severity, duration, and survival [132]. Patients with COVID-19 had low counts of both helper (Th) cells and regulatory T cells, with a more pronounced decrease in severe COVID-19 cases. Moreover, the relative percentage of naive Th cells increased and memory Th cells decreased in severe cases [62, 133]. Several studies showed COVID-19 infection to be associated with functional exhaustion of cytotoxic lymphocytes [107, 134]. An immune profile demonstrating robust activation and proliferation of CD4+ T cells along with highly activated or exhausted CD8+ T cells was associated with increased disease severity [9].

An appropriate T-cell response is important for management of acute COVID-19 infection but also for the development of immune memory. Therefore, a baseline impaired T-cell immunity may distinctively affect both the severity and the clearance of COVID-19. Several studies evaluated the counts and functionality of T cells specifically in HM patients. In the prospective CAPTURE study, longitudinal immune profiling was integrated with clinical data of patients with cancer. While SARS-CoV-2-specific CD4+ T cells were detected less frequently in HM compared to SM patients (41% vs. 81%), CD8+ T cells were detected at similar frequencies (53% and 48%) across both malignancy types. The levels of SARS-CoV-2-specific T cells were higher in patients with lymphomas versus leukemias [60, 61].

Huang et al. [135] performed flow cytometric and serologic analyses of 106 cancer patients and compared those to 113 noncancer controls. High-dimensional analysis of flow cytometric data was used to define several distinct immune phenotypes. An immune phenotype

characterized by CD8+ T-cell depletion was associated with a high viral load and the highest mortality (71%) among all cancer patients. In contrast, despite impaired B-cell responses, patients with HM and preserved CD8+ T cells had lower viral loads and mortality. Furthermore, HM patients who were treated with anti-CD20 therapy but had adequate CD8+ T cells did not suffer from increased mortality compared to other HM patients in spite of almost complete abrogation of SARS-CoV-2-specific antibodies [135].

The significance of functioning T-cell immunity was further elucidated in a large study including three cohorts of cancer patients with COVID-19 in which patterns of immune responses were correlated with clinical and serological variables [60, 61]. COVID-19 patients with HM had significantly lower counts of CD4+ and B cells, as well as low circulating Th and plasmablast responses (both critical in the generation of effective antibody responses) than SM patients, noncancer patients, and healthy persons without COVID-19, but had preserved and highly activated CD8+ T cells. Notably, 77% of HM patients had detectable SARS-CoV-2-specific T-cell responses. Mortality and disease severity were lowest in patients with robust CD4+ and CD8+ T-cell responses and highest in patients with depleted T cells, despite effective production of SARS-CoV-2-specific antibodies. These findings suggest that T-cell activation may potentially compensate for blunted humoral immune responses in patients with HM and impaired humoral immunity [60, 61].

Recipients of HCT and CAR T-cell therapy constitute a unique population of patients with HM, due to their immune dysregulation, impairment of all immune system components, and prolonged timeline for immune reconstitution. Additionally, there is a well-established role of viral infection in modulating immune reconstitution following transplantation [39, 136].

Indeed, factors associated with T-cell impairment including allo-HCT (as opposed to autologic HCT), acute GVHD, and concurrent immunosuppressive therapy were all associated with more severe COVID-19 [39]. Development of COVID-19 within 12 months of transplantation was also associated with a higher risk of mortality among allo-HCT recipients [133]. In one study, 25 HCT or CAR T-cell therapy recipients with COVID-19 underwent immunologic profiling [40]. Absolute lymphocyte subset counts were compared to counts in the same patients prior to COVID-19 diagnosis and to a historical cohort of HCT recipients from the prepandemic era. COVID-19 was associated with lower lymphocyte counts, particularly in the T-cell compartment. Detailed T-cell

phenotyping showed patterns suggestive of cytotoxic lymphocytes exhaustion. This may explain why some HCT recipients with COVID-19 infection are unable to mount an adequate antiviral response. To note, in this series, lymphocyte counts improved and immune reconstitution occurred within a short period of time after resolution of COVID-19 symptoms [40].

Conclusions

Patients with HM are at an increased risk for more protracted but ultimately severe presentation, higher mortality, and prolonged viral shedding when infected with COVID-19, even in comparison to other populations that are immunosuppressed. Evidence presented above supports the notion that the immunomodulatory effect of HM, more than the effects of their various treatments, accounts for most of this increased risk. Dysfunction of humoral immunity (particularly among patients with MM, CLL, or those treated with aCD20) and cellular immunity (particularly among patients with severe depletion of CD8+ cells' or Th cells' dysfunction such as CAR T cell and allo-HCT) seems to explain much of the excessive risk. While many treatment options evaluated for COVID-19, particularly those targeting CRS pathways, are common treatments in HM, none were specifically evaluated in this population. Our understanding of the immunopathology of COVID-19 has greatly benefited from the study of patients with HM. Patients with HM should be included in future RCTs assessing treatments for COVID-19.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was provided for this study.

Author Contributions

A.S. and A.N. guided the scope of this review and directed search strategies. A.S. and I.G. performed the search and independently assessed the eligibility of included findings. All authors participated in writing, reviewed, and approved the final version of this publication.

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