Clinical and Experimental Medicine (2024) 24:119
https://doi.org/10.1007/s10238-024-01381-5

REVIEW

# Managing and treating COVID-19 in patients with hematological malignancies: a narrative review and expert insights

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Received: 8 April 2024 / Accepted: 18 May 2024


## Abstract

Patients with hematologic malignancies (HMs) are at a significantly higher risk of contracting COVID-19 and experiencing severe outcomes compared to individuals without HMs. This heightened risk is influenced by various factors, including the underlying malignancy, immunosuppressive treatments, and patient-related factors. Notably, immunosuppressive regimens commonly used for HM treatment can lead to the depletion of B cells and T cells, which is associated with increased COVID-19-related complications and mortality in these patients. As the pandemic transitions into an endemic state, it remains crucial to acknowledge and address the ongoing risk for individuals with HMs. In this review, we aim to summarize the current evidence to enhance our understanding of the impact of HMs on COVID-19 risks and outcomes, identify particularly vulnerable individuals, and emphasize the need for specialized clinical attention and management. Furthermore, the impaired immune response to COVID-19 vaccination observed in these patients underscores the importance of implementing additional mitigation strategies. This may include targeted prophylaxis and treatment with antivirals and monoclonal antibodies as indicated. To provide practical guidance and considerations, we present two illustrative cases to highlight the real-life challenges faced by physicians caring for patients with HMs, emphasizing the need for individualized management based on disease severity, type, and the unique circumstances of each patient.

**Keywords** COVID-19 · Omicron · Hematological malignancies · Immunocompromised · Immunosuppressed · Lymphomas

## Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has significantly impacted public health worldwide. Infection rates, morbidity, and mortality have varied across geographic regions and time periods, characterized by successive waves of infections driven by emerging variants [1–6]. Data indicate a general decrease in mortality and disease severity with each wave, except for the Delta variant-dominant wave, which had higher mortality rates [1, 3, 7, 8]. On the other hand, the Omicron wave has been associated with less severity and mortality, potentially due to the variant itself or to acquired immunity from prior infection or vaccination, both of which have shown to substantially decrease the risk of severe infection in later waves [8].

Certain risk factors consistently linked to infection severity or mortality includes advanced age, male sex, and the presence of comorbidities [3, 4, 9]. A particularly vulnerable group includes individuals with HMs, which encompass cancers of the blood including leukemias, lymphomas, and myelomas [10]. As a group, HMs are the fourth most frequently diagnosed type of cancer in both men and women [11], affecting approximately 1.3 million individuals worldwide [12]. Impaired immune regulation in HM patients, compounded by immunosuppressive treatments, places them at increased risk for life-threatening infection [13].

Although the world has transitioned to an endemic state, clinicians should remain vigilant when managing HM patients, and understanding the ongoing implications and

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Published online: 04 June 2024

risks associated with COVID-19 remains as important as ever. Studies reported that while COVID-19 infection rates in HM patients are comparable to the general population, significant differences exist in morbidity and mortality [14–16]. Notably, elderly individuals with HMs are particularly vulnerable due to their advanced age and increased risk of contracting nosocomial infections from assisted living or healthcare facilities [17].

This paper offers a comprehensive review of the impact of COVID-19 on individuals with HMs utilizing a combination of literature analysis and expert experience. We examine key clinical aspects, including the risks of severe COVID-19 influenced by different HM subtypes and clinical factors, as well as the impact of cancer treatments on COVID-19 outcomes and vaccine-induced seroconversion and protection levels. Considering the rapidly evolving disease landscape along with the accumulation of experience and knowledge, we also discuss the various prophylactic and therapeutic options for the clinical management of HM patients. We presented two hypothetical patient scenarios that shed light on the complexities and considerations involved in the care of HM patients. Drawing on real-life insights from an international group of experts, our manuscript aims to provide a highly practical review, offering insights and best practices for effectively addressing the ongoing threat of COVID-19 among individuals with HM.

## Understanding the impact of HM on COVID-19-related risks

Studies consistently indicate that individuals with HMs are at higher risks of severe COVID-19 infection, secondary infections, and hospitalizations compared to the general population [18, 19]. Moreover, compared to individuals with solid tumors, those with HMs had a greater susceptibility to severe or moderate COVID-19 [20], possibly due to the depletion of antibodies and antibody-producing B cells associated with HMs [21].

A meta-analysis reported an approximate 25% mortality rate among HM patients hospitalized for COVID-19 [22]. Several factors contribute to the elevated all-cause mortality in this group, including direct infection, lymphopenia, interruption of cancer treatment, immunosuppression due to treatments, and secondary infections. While the general population experienced decreased COVID-19 mortality rates from the initial phase to the phase dominated by the Omicron variant [1], this decline was not initially observed in individuals with HMs until widespread vaccination [23–25]. Throughout the pandemic, HM patients consistently exhibited higher mortality rates compared to both the general population and individuals with solid tumors [20–22].

## COVID-19-associated thrombosis and complications in HMs

Patients with HMs and COVID-19 have higher morbidity and mortality; however, the underlying pathophysiological mechanisms remain unclear. It has been postulated that endothelial injury plays a central role in the pathogenesis of acute respiratory distress syndrome and organ failure in severe COVID-19 [26]. Moreover, COVID-19 is associated with complex coagulation abnormalities, leading to a hypercoagulable state and thrombosis [26, 27]. Stasis, common in hospitalized or critically ill patients, irrespective of COVID-19, is a well-known contributor to the development of venous thromboembolism (VTE) [27]. Patients with COVID-19 exhibit various prothrombotic factors, including elevated factor VIII, as well as laboratory abnormalities indicating increased fibrinogen and D-dimer levels [27]. This phenotypic hypercoagulable state has been referred to as "COVID-19-associated coagulopathy or thromboinflammation" [28]. In parallel, cancer itself is associated with a hypercoagulable state and a significantly higher incidence of thromboembolic complications [26, 27]. Therefore, the combination of HM and COVID-19 may amplify this risk, resulting in overall poor outcomes [26, 27].

A retrospective study of HM patients reported statistically significant higher rates of composite thrombotic outcomes (cerebrovascular accidents + VTE) compared to the general population [27]. Independent of disease status, HM patients also exhibited a significantly increased need for intensive care and respiratory support, and had higher fatality rates [27]. Based on these findings, it is recommended that patients with HM be treated with anticoagulation strategies to mitigate the risk of thrombotic complications and optimize patient outcomes. The latest American Society of Hematology guidelines recommend prophylactic-dose anticoagulants for COVID-19 patients needing ICU care in the absence of contraindications, over intermediate or therapeutic doses, as VTE prophylaxis, consistent with other international recommendations from the US National Institutes of Health COVID-19 Treatment Guideline, the World Health Organization Living Guidance document, and the International Society on Thrombosis and Haemostasis [29].

In the following, we present an illustrative case scenario that exemplifies the increased risk of severe COVID-19 and the associated complications faced by a HM patient undergoing chemotherapy.

## Illustrative cases

*The case scenarios presented are for illustrative purposes only and do not represent specific individuals. They are

hypothetical scenarios derived from the authors' collective clinical experience.

## Scenario 1–An elderly patient with marginal zone lymphoma

### Background

A 70-year-old male was diagnosed with Stage 4E marginal zone B cell lymphoma involving the kidney and bone marrow. He completed guideline-recommended treatment with 6 courses of the rituximab-bendamustine combination in October 2021, resulting in complete remission. Subsequently, he received rituximab maintenance therapy every 8 weeks, completing his second cycle in March 2022. He had received 3 doses of COVID-19 mRNA vaccine.

### COVID-19 clinical management

The patient experienced three separate COVID-19 infections, as described in Fig. 1. The first time, he received treatment with molnupiravir and recovered. However, he was subsequently tested positive for COVID-19 on follow-up and developed a fever. As a result, the planned third course of rituximab maintenance therapy was deferred. The patient was transferred to a COVID-19-specialized hospital for further treatment. There, he was treated for severe COVID-19 infection, pulmonary aspergillosis, and multidrug-resistant Klebsiella pneumoniae. Shortly after discharge, the patient returned to the clinic with episodes of dyspnea and fever and tested positive for COVID-19 once again. The patient was treated with additional medications and requested home isolation.

### Resolution of COVID-19 and current status

On follow-up assessments, the patient was clinically stable but had shortness of breath with activities and required considerable assistance. His marginal zone lymphoma remained in remission. Chest CT showed worsened lung fibrosis and ground-glass opacities.

Currently, the patient is considerably stable, with weight gain, and has no more shortness of breath. Rituximab maintenance therapy was discontinued to prevent further immunosuppression.

### Summary

This case highlights the heightened vulnerability of a patient with HM to severe COVID-19 disease, further compounded by age, as evidenced by multiple recurrent

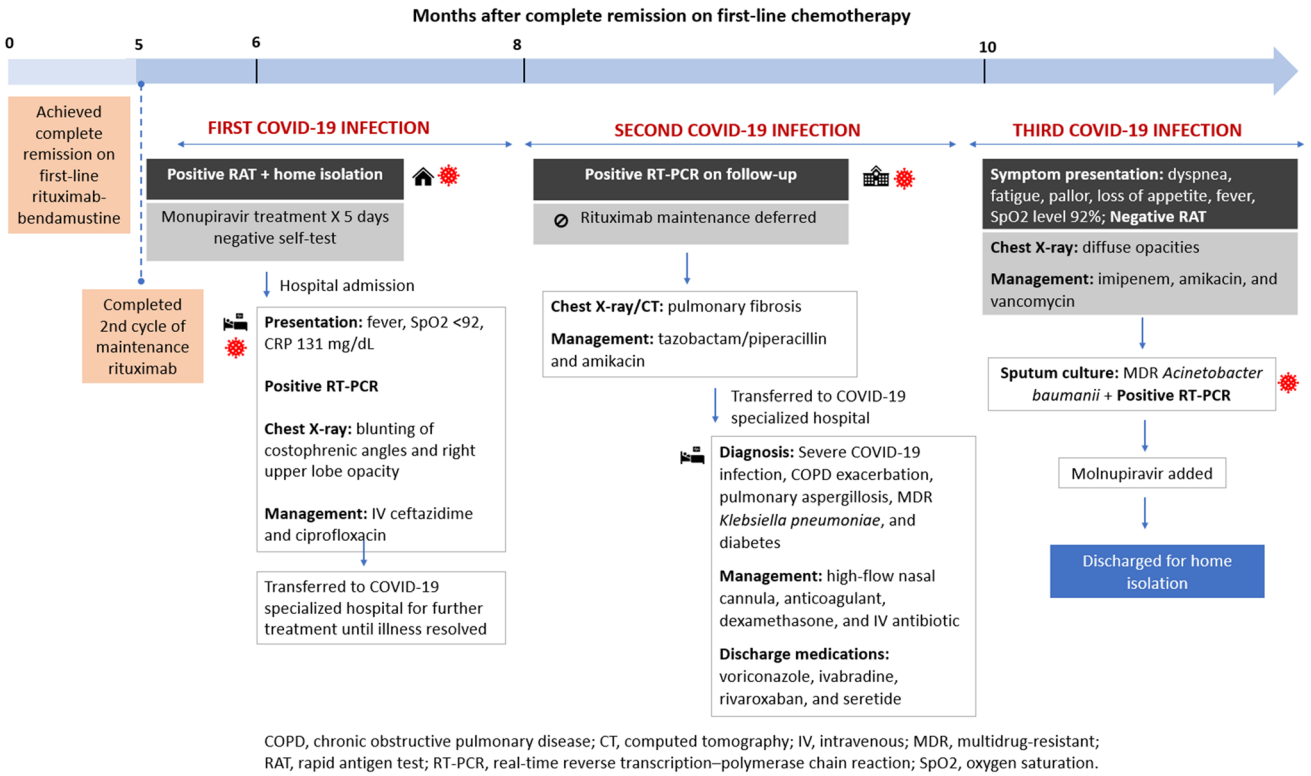


**Fig. 1** Summary of COVID-19 clinical history/timeline

infections and failure of virus clearance. The patient experienced severe secondary conditions, including pneumonia, resulting in long-term lung damage. The case emphasizes that the severity of COVID-19 extends beyond the acute phase, as immunocompromised individuals remain at risk even after completing chemotherapy and transitioning to maintenance therapy. Therefore, careful outpatient monitoring and up-to-date vaccinations are crucial. Considering the patient's susceptibility to infections and ongoing cancer remission, the decision was made to withhold rituximab maintenance to prevent further immunosuppression.

## Impact of COVID-19 on different types of HM

The impact of COVID-19 on individuals with HMs differs from those without HMs and even individuals with solid tumors. Further examination focusing on different types of HMs (Fig. 2) is necessary to understand the potential varying effects of COVID-19 on these patients and to develop appropriate strategies for managing and preventing adverse outcomes.

### Chronic myeloid leukemia (CML)

CML patients typically require lifelong therapy with tyrosine kinase inhibitors (TKIs), which is linked to suppression of the innate and adaptive immune system [30]. Immune dysfunction is particularly pronounced at diagnosis [30]. The impact of targeted cancer treatments like TKIs on vaccination response and inhibition of B cell function and antibody response is also well documented [41].

Surprisingly, the incidence of COVID-19 infection in individuals with CML was relatively low, ranging from 4.1 to 6.7% across studies [52, 53]. Reported COVID-19 mortality varied, with some studies indicating lower rates compared to the general population and others reporting higher [42, 52, 53]. Data from earlier in the pandemic showed that active treatment with TKIs, particularly imatinib, was linked to reduced COVID-19 incidence and mortality, implying a potential protective effect [43].

The decreased incidence of COVID-19 in individuals with CML receiving active TKI treatment may be attributed to the resolution of immune deficiencies caused by the malignancy, which occurs within a few weeks of initiating treatment [33]. Further investigations suggest that TKIs may also play a role in reducing the impact of COVID-19

| | Chronic myeloid leukemia (CML) | Multiple myeloma (MM) | Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) | Acute leukemia (AML and ALL) |
|---|---|---|---|---|
| **Disease characteristics** | • Characterized by accumulation of immature myeloid cells and suppression of the innate and adaptive immune system<br>• Accounts for approximately 15% of new cases of leukemia worldwide each year<br>• Disease remission can be induced and maintained with long-term TKIs | • Characterized by malignant proliferation of plasma cells, leading to impaired production of antibodies and compromised humoral and cellular immunity<br>• Estimated annual worldwide incidence of 160,000 and mortality of 106,000 | • HL primarily affects cervical lymph nodes, with an annual incidence of approximately 80,000 globally. Represents approximately 0.4% of new cancer cases and 0.2% of cancer-related deaths annually<br>• NHL is a heterogeneous group of lymphoid tissue cancers. Approximately 545,000 new cases of NHL and 260,000 deaths each year | • In AML, uncontrolled proliferation of immature blast cells in the peripheral blood and bone marrow results in ineffective erythropoiesis and bone marrow failure. Accounts for approximately 80% of adult leukemia cases<br>• ALL is characterized by the uncontrolled proliferation of early lymphoid precursors that infiltrate the bone marrow and can spread to extramedullary sites |
| **Common treatment modalities** | • Targeted therapy with TKIs to disrupt the cellular pathways and molecular drivers that regulate cancer cell growth | • Combination of immunomodulatory drugs, proteasome inhibitors and dexamethasone with or without transplant | • Immunosuppressive chemotherapy regimens that deplete T cells, or B cell-depleting immunotherapies | • Targeted therapies (e.g. FLT2-inhibitors in AML, TKIs in ALL), antibody/immunotherapies such as blinatumomab or gemtuzumab ozogamicin |
| **COVID-19-related risks** | • Patient factors include advanced age, hypertension, diabetes, dyslipidemia, arterial disease, and chronic obstructive pulmonary disease/emphysema<br>• Immunological impairment and treatment-related adverse events including anemia and neutropenia<br>• Disruptions due to the pandemic including enrollment in clinical trials, medication delivery, and interruption of CML treatments due to COVID-19 infection<br>• Administration of TKIs interrupted in up to 30% of CML patients with COVID-19 | • Patient factors include diabetes, hypertension, chronic kidney disease and liver disease, and poor disease control of MM<br>• Cytopenia as a common side effect increases risk of COVID-19 infection<br>• Hypogammaglobinemia and immunosuppression linked to increased mortality<br>• Disruptions due to the pandemic led to treatment delays, low participation in clinical trials, and delayed treatment for patients not requiring hospitalization (55%) and who had recovered from COVID-19 (63%) | • High mortality rates observed in patients with comorbidities such as diabetes and obesity<br>• Underlying hypogammaglobulinemia, neutropenia, depletion of B cells and T cells due to immunosuppressive therapies such as anti-CD20 antibody therapies, active disease, and recent HSCT linked to worse COVID-19 outcomes | • Severe immunosuppression related to underlying disease, aggressive therapies, neutropenia<br>• Active or uncontrolled malignancy, cardiovascular and metabolic comorbidities, older age and ongoing or recent AML treatment (<3 months before COVID-19 infection) linked to increased mortality |

**Fig. 2** Summary overview of HM disease characteristics, common treatment modalities, and COVID-19-related risks [30–51]

by inhibiting viral fusion to host cells [54], as previously demonstrated against other coronaviruses such as SARS-CoV and MERS-CoV [55, 56]. Additionally, TKIs have been found to upregulate key antiviral genes and downregulate proviral genes associated with the immune system [54], supporting their potential role in combating COVID-19 infection beyond their anticancer effects in CML patients. Therefore, despite their partly immunosuppressive function [41], TKIs appear to have a protective role against COVID-19, suggesting that TKI treatment should not be interrupted for CML patients with COVID-19 [33].

### Multiple myeloma (MM)

In MM, impaired antibody production and compromised immunity, coupled with treatment-related side effects such as cytopenia, increase susceptibility to respiratory infections like COVID-19 [57–59].

Larger evaluations have consistently shown higher rates of COVID-19 infection, hospitalization, and mortality in MM patients compared to those without cancer [36]. In contrast to the general population, COVID-19 survival rates in MM patients did not improve between the first and second waves [36], and the high COVID-19 mortality rate (ranging from 24 to 55%) [60] has been linked to hypogammaglobinemia and immunosuppression [57, 61].

The impact of anticancer treatments on COVID-19 outcomes in MM patients has been inconclusive. While some studies showed no negative outcomes and robust immune responses in MM patients receiving anticancer treatments [58, 61, 62], others indicated a higher risk of severe COVID-19 symptoms with active MM therapy [63, 64]. Findings on the anti-CD38 antibody daratumumab in relation to COVID-19 severity and complications have been mixed [61, 64]. Proteasome inhibitors and corticosteroids have been associated with an increased risk of severe COVID-19 outcomes, including ICU admissions and mechanical ventilation [45, 65, 66]. On the other hand, stem cell transplant within a year of infection does not appear to increase the risk of severe COVID-19 outcomes and, in some cases, shows more favorable outcomes [36, 45, 58, 67, 68].

### Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL)

Lymphomas, characterized by hypogammaglobulinemia, neutropenia, and depletion of B cells and T cells, place patients at heightened risk of infections like COVID-19 [39, 40].

Individuals with NHL have shown a higher COVID-19 incidence compared to other HMs [15, 69, 70]. Particularly, NHL patients requiring hospitalization were more likely to experience severe respiratory deterioration [70]. In an Italian cohort study, lymphoma patients had a high fatality rate of 33% due to COVID-19 [40]. Among different lymphoma subtypes, HL patients exhibited more favorable survival rates, primarily attributed to their significantly younger age, as supported by existing literature. Additionally, patients who received an initial lymphoma diagnosis 3 or more years before COVID-19 infection experienced better clinical outcomes and lower fatality, providing valuable insights for identifying patients for early vaccination strategies [40].

Active disease at the time of COVID-19 infection or progressive lymphoma status is the strongest predictors of death [39]. Treatment with anti-CD20 immunotherapy within 12 months of COVID-19 diagnosis has been associated with poorer outcomes, including longer hospitalization and increased mortality compared to individuals not receiving B cell-depleting therapies [71]. Lymphoma patients who have undergone hematopoietic stem cell transplantation (HSCT) also showed prolonged COVID-19 infection [71].

Considering these findings, careful monitoring and longer-term clinical follow-up are warranted to assess the impact of lymphoma and its treatment on immunity and COVID-19 outcomes. Patients should receive optimal treatment for their underlying disease, with a focus on achieving disease remission to improve outcomes [39].

### Acute leukemias (AML and ALL)

To date, there is limited data on COVID-19 in adult patients with acute leukemia (AL) particularly in relation to acute myeloid leukemia (AML) and (ALL). Effective management of patients with AL and concurrent COVID-19 necessitates close interdisciplinary collaboration between hematologists and infectiologists. On one hand, newly diagnosed AL requires prompt initiation of chemotherapy [50]. On the other hand, intensive therapy may increase the risk of severe COVID-19 [50]. Therefore, careful consideration is needed when determining the systemic treatment approach.

Pre-vaccination and pre-Omicron era data from the European Hematology Association Survey indicate a high COVID-19-related mortality rate of 40% in adult AML and 26% in adult ALL patients [72]. Other registry studies also support the elevated COVID-19 mortality observed in AML patients [50]. However, large data sets are lacking for adult ALL patients with COVID-19 due to the low ALL incidence in adults [50]. The impact of COVID-19 infections on AL treatment is rarely reported; however, available evidence suggests that treatment delay did not increase the risk of relapse, whereas therapy discontinuation was linked to worse outcomes in AML patients [50, 73]. Therefore, it is recommended to delay systemic treatment in AL patients with COVID-19 until SARS-CoV-2 negativity, unless immediate treatment is required [50]. These patients should

receive early antiviral therapy to prevent disease progression and enable rapid elimination of the virus [50].

## Clinical factors linked to COVID-19 outcomes in HMs

### Types of immunotherapies

Since the start of the pandemic, the effects of immunosuppression resulting from HM treatments on COVID-19 outcomes have been a concern. Emerging evidence indicates that the effects of immunosuppressive treatments vary. Although certain HM treatments are known to induce neutropenia, it has been suggested that neutropenia may not be entirely detrimental in COVID-19 cases, as neutrophils are likely mediators of COVID-19-related pulmonary damage [74]. Additionally, certain immunosuppressants, like TKIs, may offer some potential benefits through antiviral activity [43, 54]. On the other hand, B cell-suppressing immunotherapies [71], chemotherapy regimens like platinum plus etoposide, or DNA methyltransferase inhibitors, have been shown to negatively impact COVID-19 outcomes [75].

Multiple studies indicated worse outcomes for HM patients on immune-suppressing chemotherapy in the 1–3 months prior to contracting COVID-19, including higher hospitalization, ICU admissions, mechanical ventilation, and death [22, 24, 76]. However, the impact of recent systemic anticancer therapies on COVID-19 outcomes is complex, with mixed findings [77, 78]. Some studies suggested increased mortality risk with systemic conventional chemotherapy, but not with monoclonal antibody or molecular-targeted therapies [24]. Specific regimens, including R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), platinum plus etoposide, and DNA methyltransferase inhibitors, were associated with particularly high all-cause mortality rates (> 40%) [75]. Additionally, significant mortality rates were observed in HM patients receiving systemic corticosteroid therapy.

Altogether, these findings underscore the importance of considering specific COVID-19 prevention measures and carefully managing treatment regimens. While discontinuing anticancer treatment can lead to worsened outcomes, certain therapies carry a heightened risk of COVID-19 mortality.

### Immunologic factors related to COVID-19-related mortality in HMs

Immunologic factors related to COVID-19 outcomes and mortality have attracted significant research interest. Lymphocytes, particularly CD8+ T cells, are known to play a crucial role in COVID-19 recovery [21, 79, 80]. Lymphopenia is common in patients with severe COVID-19 and is a known predictive factory for mortality [81]. In patients with lymphoid malignancies, impaired CD8+ T cell immunity, driven by B cell depletion, was associated with persistent COVID-19 infection, and individuals with low T cell counts (CD8+ < 50 cells/μL or CD4+ < 100 cells/μL) had markedly poorer outcomes, including higher 60-day mortality rates [79]. Severe lymphopenia was also associated with higher risks of secondary infections within 48 h after hospital admission, contributing to increased mortality [81]. Among HM patients, those who developed secondary infections had a markedly higher 30-day mortality rate compared to those without secondary infections (69% vs. 15%, $p < 0.001$) [82].

HM patients are particularly vulnerable due to immune cell depletion, including CD8+ T cells and B cells, caused by underlying malignancies and immunosuppressive therapies [21]. Moreover, disruptions to cancer treatments during the pandemic, either as a protective measure or due to COVID-19 complications, are associated with decreased survival post-infection [83, 84].

In a prospective cohort study, patients with solid tumors exhibited similar immunologic profiles to patients without cancer during acute COVID-19, while patients with HM showed significant impairments in B cell function and SARS-CoV-2-specific antibody responses [21]. Interestingly, despite the impaired humoral immunity and higher mortality in HM patients with COVID-19, improved survival rates were observed in those with higher CD8+ cells, including individuals on anti-CD20 therapy [21]. Notably, 77% of HM patients demonstrated detectable SARS-CoV-2-specific T cell responses, underscoring the crucial role of cellular immunity when humoral responses are compromised [21]. This finding is promising because current COVID-19 mRNA vaccines induce robust CD8+ T cell responses alongside humoral responses [21]. It is important to note that both B cell-depleting therapies and cytotoxic chemotherapy agents, which can impact the T cell compartment, are mainstays of treatment in lymphoma [21]. Therefore, treatment decisions should carefully weigh the risk of immune dysregulation against the benefits of disease control, particularly in non-curative settings.

### Impact of B cell versus T cell depletion

A study comparing COVID-19 outcomes in individuals with HMs who had prolonged infection found that T cell-depleting therapies were associated with increased COVID-19 mortality, while B cell-depleting therapies were linked to rehospitalization and prolonged COVID-19 infections [79]. The complex interaction between B cells and T cells may explain these findings, as B cells rely on CD4+ T cells for maturation [79].

B cells are crucial for immune defense against viral infections, producing viral-specific antibodies and triggering cytokine responses important for clearing infections like SARS-CoV-2 [85]. Secondary immunodeficiency commonly occurs in HMs and often affects B cells [86]. In advanced HMs such as CLL, MM, and certain forms of NHL, dysregulation of immune cells results in B and T cell depletion and hypogammaglobulinemia. Treatments for these HMs, including monoclonal antibodies targeting B cell epitopes, have been linked to poorer COVID-19 outcomes [86]. Particularly, evidence consistently demonstrates the impact of anti-CD20 agents, such as rituximab, in inducing rapid B cell depletion, resulting in prolonged COVID-19 courses characterized by persistent SARS-CoV-2 replication [71]. Blinatumomab, a bispecific CD19-directed T cell engager, is used for treatment of ALL can also impair B cell response and causes hypogammaglobulinemia [87]. There are currently no specific recommendations regarding SARS-CoV-2 and blinatumomab, so the decision to withhold therapy should consider its risks and benefits.

## Scenario 2–A patient with B-ALL on blinatumomab

### Background

A 55-year-old female with no significant past medical history was diagnosed with B cell ALL in August 2022. She received one cycle of intensive induction chemotherapy which was complicated by severe fungal infection, precluding her from further intensive chemotherapy. She was subsequently switched to blinatumomab for further treatment of her B-ALL.

### COVID-19 clinical management

In May 2023, she tested positive for COVID-19 during her second cycle of blinatumomab infusion. She presented with fever, cough, and rhinorrhea but did not require oxygen therapy. Chest X-ray was clear. She had previously received three doses of mRNA vaccine (last dose in May 2022). She was admitted for monitoring and received a 5-day course of intravenous remdesivir with improvement of her symptoms. She was discharged on day 5 of hospital admission with no major complications. However, her COVID-19 took up to 5 weeks to fully resolve, as indicated by persistent weekly positive results on nasopharyngeal COVID-19 PCR swabs. As a result, her cancer treatment had to be delayed.

### Summary

This case underscores the challenges faced by patients undergoing immunosuppressive cancer treatment, including the increased risk of severe outcomes, such as hospitalization and susceptibility to secondary infections, due to both the treatment itself and inadequate protection from COVID-19 vaccinations. Despite completing the full course of COVID-19 vaccination, they may still face an elevated risk of persistent COVID-19, with prolonged symptoms and positive PCR tests, likely due to impaired immune responses. These complications not only prolong the illness but also result in delays in HM maintenance treatment.

## COVID-19 management in individuals with HMs

### Vaccination

Vaccination is a significant component in the COVID-19 armamentarium, with proven efficacy in reducing transmission, hospitalizations, and deaths due to severe COVID-19 in the general population. However, concerns have been raised regarding its effectiveness in individuals with HMs, as well as waning immunity over time [88, 89]. While multiple vaccines have been developed, studies primarily focus on mRNA-based vaccine use in immunosuppressed and HM patients [88]. Initial reports have indicated lower seroconversion in individuals with HMs following COVID-19 vaccination, attributed to impaired humoral immunity and the effects of immunosuppressive therapies (Fig. 3) [88, 89].

| Clinical factors including disease biology and immunosuppressive treatment impacting response to COVID-19 vaccination |
|---|
| ○ Baseline malignancies such as B cell NHL<br>○ Recent or active treatment during time of vaccination, such as ongoing anti-CD20 antibody therapy or within 6–12 months from the last dose<br>○ Profound hypogammaglobulinemia (<4 g/L), severe lymphopenia (<500 cells/μL) [10–12]<br>○ BCMA targeted bispecific monoclonal antibody<br>○ Induction chemotherapy for acute leukemia<br>○ CAR T treatment |

**Fig. 3** Factors identified to be associated with poor COVID-19 vaccine response [89–93]

A systematic review found seroconversion rates ranging from 54 to 85% in HM patients after receiving two vaccine doses, compared to nearly 100% in healthy controls or from 85 to 94% in individuals with solid tumors [94]. Notably, those receiving B cell-depleting therapies and recent immunosuppressive treatments, including hematopoietic stem cell transplantation (HSCT), had significantly lower seroconversion rates [88, 94]. Similarly, lower seroconversion rates were observed with anti-CD20 antibodies [83, 94–96], Bruton's tyrosine kinase inhibitors (BTKIs) [83], and stem cell transplantation [95]. Earlier studies on chimeric antigen receptor T cell (CAR-T) therapy and bispecific antibodies have demonstrated variable SARS-CoV-2-specific B and T cell responses in patients with MM [97, 98]. Particularly, patients undergoing active treatment with anti-CD38 and anti-B cell maturation antigen (BCMA) antibody-based therapies showed an unexpected absence of T cell responses and anti-spike antibodies post-vaccination compared to those not on active treatment [97, 98]. Additional studies confirmed that only a minority (~30%) of MM and NHL patients receiving CAR-T had clinically relevant antibody responses (>250 IU/mL) [99]. On the other hand, immune checkpoint inhibitor therapies or hormonal therapies did not appear to impact vaccine efficacy, as individuals with HMs receiving these treatments demonstrated seroconversion rates of 97% and 100%, respectively [95].

Despite the lower seroconversion rates observed in HM patients, substantial evidence supports the clinical benefit of COVID-19 vaccination, with emerging data indicating a dose–response relationship [89, 100]. A higher number of vaccine doses received before COVID-19 infection is associated with significantly lower mortality rates, highlighting the benefit of booster doses in providing optimal protection to this vulnerable group [89]. CAR-T recipients showed improved serological response rates with each additional vaccine dose, reaching 75% after four doses compared to 20.4% after one dose [9]. Furthermore, anti-spike antibody titers were more than 30 times higher after four doses compared to two doses [100]. Based on emerging data and the evolving context of COVID-19, revised vaccination recommendations for patients with HM and HSCT (Table 1) now include a three-dose primary schedule followed by an additional vaccine dose. [90] The administration of a fourth vaccine dose has been shown to be safe and effective in increasing antibody titers [90]. It is crucial to prioritize timely vaccination without delaying the treatment of underlying diseases, and even patients with expected poor response, such as those on therapy with anti-CD20 antibodies, may still benefit from vaccination [90].

## Prophylactic measures

To enhance COVID-19 prevention in HM patients, it is crucial to uphold strict infection control measures, including hand hygiene, physical distancing, and ventilation of room [90]. The ECIL 9 guidelines highlight that it is essential for health personnel to utilize personal protective equipment, and patients should be placed in single rooms, avoiding positive pressure rooms, to effectively prevent transmission [88, 90].

Given the unpredictable or inadequate immune response to COVID-19 vaccination in HM patients, passive immunization strategies via pre- or post-exposure prophylaxis have shown to be valuable options for providing added protection to this vulnerable population [101]. These strategies involve the use of various anti-spike monoclonal antibodies, such as tixagevimab-cilgavimab, casirivimab-imdevimab, and bamlanivimab-etesevimab, which work by binding to the SARS-CoV-2 spike protein and preventing viral entry into host cells [102].

In a large placebo-controlled randomized controlled trial, tixagevimab-cilgavimab administered as pre-exposure prophylaxis reduced the risk of developing symptomatic COVID-19 by 76.7% for a median of 83 days post-administration among high-risk patients with poor vaccine response [103]. The effectiveness of casirivimab-imdevimab as post-exposure prophylaxis was assessed in unvaccinated individuals who had been in contact with COVID-19 patients. Compared to placebo, casirivimab-imdevimab administered 96 h

**Table 1** Updated recommendations of ECIL 9 (European Conference on Infections in Leukemia) on vaccinations for COVID-19 in HM and HSCT patients [90]

| Key highlights of vaccination recommendations for HM patients including HSCT and CAR-T cell recipients |
|---|
| A three-dose primary schedule of mRNA vaccine is recommended; additional booster dose(s) or mRNA vaccine should be considered after at least 3 months from the 3rd dose |
| The interval between a COVID-19 infection and subsequent boosters should be at least 3, and preferably 4 months |
| For HSCT recipients, additional doses can help improve immune response by increasing seroconversion and antibody levels. Therefore, booster doses are encouraged, preferably with the new updated bivalent vaccines targeting original strains and new Omicron subvariants. The risk of worsening/eliciting graft-versus-host disease should be considered when planning vaccination schedule |
| For CAR-T cell recipients, patients with B cell aplasia are unlikely to mount an antibody response; however, repeated vaccine doses might provide some benefit |

after diagnosis was associated with a lower risk of symptomatic COVID-19 (1.5% vs. 7.8%) [104].

However, it is important to note that studies on monoclonal anti-S antibodies as prophylactic strategies were mostly conducted before the predominance of the Omicron variant, particularly the newer BA.4/5 subvariants [101]. The neutralizing efficacy of casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab against BA.4/5 is significantly reduced to maintain clinical efficacy, while the efficacy of tixagevimab/cilgavimab is moderately reduced [101]. Preliminary data suggest doubling the dosage of tixagevimab/cilgavimab in the presence of less susceptible omicron subvariants may increase efficacy [105]. Considering these findings, it is important to evaluate each patient case's individually, and pre-exposure prophylaxis should not be used as a substitute for vaccination when successful vaccination is feasible [90, 101]. Monoclonal anti-spike antibodies for pre- and post-exposure prophylaxis can be considered if they demonstrate activity against circulating variants [90].

## Treatment

The treatment options for COVID-19 are constantly evolving. Several crucial factors need to be considered when determining treatment strategies for HM patients with COVID-19, including the patient's immune status, prior COVID-19 vaccinations and anticipated vaccine response, severity of COVID-19, local epidemiology and presence of VOCs, as well as the availability of anti-COVID-19 drugs [101]. Treatment strategies are tailored based on the differentiation of disease severity and taking into account the scale of clinical progression, ranging from mild outpatient cases to moderate or severe hospitalized cases [90, 101]. Table 2 provides a summary of currently used therapies. The importance of early treatment initiation cannot be overstated.

**Mild–moderate disease** For patients with mild-to-moderate disease, antivirals and monoclonal antibodies are effective options for early therapy [90, 101]. Randomized controlled trials have demonstrated the effectiveness of initiating these treatments within 3–7 days from symptom onset in reducing hospitalization or death in unvaccinated outpatients with mild or moderate COVID-19 or those at high risk for severe disease [90, 101]. Although HM patients constituted only a small minority in these trials, observational studies support the notion that this population can benefit from these treatments [90, 106]. Moreover, since most of these trials exclude vaccinated patients, the evidence can be best extrapolated to cancer patients who are either unvaccinated or expected to have an inadequate vaccine response [101].

Monoclonal antibodies or antibody combinations, including casirivimab/imdevimab, bamlanivimab/etesevimab, regdanvimab, sotrovimab, and tixagevimab/

**Table 2** Summary of current treatment options for patients with COVID-19. List based on the latest ECIL 9 and Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology guidelines (at time of manuscript preparation) [90, 101]

| | Mild COVID-19 | Moderate to severe COVID-19 (requiring oxygen support; or saturation < 90–94%, respiratory rate > 30/min) | Critical COVID-19 (ARDS, sepsis, septic shock, MIV, NIV, or vasopressor therapy) |
|---|---|---|---|
| Treatment options | a) Anti-SARS-CoV-2 monclonal antibodies, if active against the circulating variants<br>b) Nirmatrelvir/ritonavir<br>c) Remdesivir<br>d) Molnupiravir<br>-Dexamethasone is not recommended in the early treatment of mild/outpatient HM patients with COVID-19 | a) Dexamethasone<br>b) Remdesivir<br>c) If patient is seronegative: monoclonal antibodies, if active against the circulating variants or high-titer convalescent plasma, if monoclonal antibodies are not accessible<br>d) If severe COVID-19 inflammation (indicated by inflammation parameters), including worsening despite dexamethasone, add 2nd immunosuppressant: Anti-IL-6 (tocilizumab, sarilumab) or JAK inhibitor(baracitinib/tofacitinib) Anti-IL 1 (anakinra) | a) Dexamethasone<br>b) Remdesivir<br>c) Monoclonal antibodies, if active against the circulating variants (no data in MIV patients)<br>d) If severe COVID-19 inflammation (indicated by inflammation parameters), add 2nd immunosupprssant with anti-IL-6 (tocilizumab, sarilumab) |

ARDS, acute respiratory distress syndrome; MIV, mechanical invasive ventilations; NIV, non-invasive ventilation

cilgavimab, have shown significant reductions in hospitalization or death (ranging from 50.5 to 85%) compared to placebo [101]. However, data on their efficacy against the Omicron variant, particularly the BA.4/5 subvariants, are primarily based on in vitro or small observational studies [101]. Therefore, antivirals remain the cornerstone of therapy as their activity is not influenced by VOCs [90]. Currently, three antiviral agents are used for early COVID-19 treatment in high-risk patients: nirmatrelvir/ritonavir, remdesivir, and molnupiravir [90, 101].

Oral nirmatrelvir/ritonavir or intravenous remdesivir are the preferred choices based on efficacy data [107, 108]. When considering nirmatrelvir/ritonavir, potential drug-drug interactions should be taken into account, and careful assessment or reduction of existing immunosuppression or targeted therapy can allow its use in most HM patients [90]. Molnupiravir use is limited by the lower efficacy in the randomized trial (relative risk reduction of 30% [109], compared to 87% of nirmatrelvir/ritonavir or remdesivir), and might not be available in some countries however offers advantages such as the absence of drug-drug interactions and the possibility of use in patients with renal failure (ClCr < 30 ml/min) [90]. It can be considered as early therapy for ambulatory patients when more potent therapeutic options are contraindicated or unavailable [90, 110].

The routine use of high-titer convalescent plasma is not supported for the treatment of mild/moderate COVID-19 [90]. However, considering its reduced susceptibility to protein-spike mutations that can lead to the loss of monoclonal antibody activity, convalescent plasma might be useful in immunocompromised patients in addition to antivirals, especially when monoclonal antibodies effective against the locally predominant variants or antivirals are not available [90].

**Moderate–severe disease requiring hospitalization or oxygen support** COVID-19 progresses through different phases, with active viral replication as the primary factor in the earlier stages and hyperinflammation becoming more prominent in later, more severe disease [101]. For the management of hospitalized HM patients with COVID-19, it is important to distinguish between moderate disease (requiring no or low-flow oxygen) and severe disease (requiring high-flow oxygen, non-invasive ventilation, or mechanical ventilation) [101]. Remdesivir can be considered for patients with moderate COVID-19 or with severe COVID-19 not yet on mechanical ventilation for up to 10 days [101]. However, COVID-19 patients, and cancer patients in particular, often experience rapid deterioration, with escalation from low-flow oxygen to mechanical ventilation within 24 h in some cases [101]. Therefore, the patient's disease course should be taken into account, and remdesivir can be combined with other adjuncts such as IL-6 or JAK inhibitors if necessary [90, 110].

Immunosuppressive agents, particularly dexamethasone, are an important part of therapy in severely ill COVID-19 patients. The benefit of dexamethasone in improving clinical outcomes and reducing mortality was demonstrated in about a fifth of patients with low- or high-flow oxygen and about a third in mechanically ventilated patients [101]. In the presence of systemic inflammation (e.g., highly elevated C-reactive protein, respiratory worsening) the addition of anti-IL-6 monoclonal antibodies such as tocilizumab or sarilumab to dexamethasone can be considered for patients on oxygen support [88, 90, 101]. Alternatively, for patients with systemic inflammation based on elevated levels of soluble urokinase plasminogen activator receptor, anti-IL-1 monoclonal antibodies such as anakinra have shown benefit. Additionally, JAK inhibitors like baricitinib and tofacitinib have demonstrated survival benefits in addition to dexamethasone by controlling inflammation in patients on oxygen support [88, 101].

## Conclusion

COVID-19 has significantly impacted the health and treatment course of individuals worldwide. While progress has been made in understanding the disease and developing vaccines and treatments that led to improvements in morbidity and mortality, individuals with HMs remain vulnerable to COVID-19-related risks and poor outcomes. It is crucial to implement comprehensive measures, including prophylactic and therapeutic options, as well as updated vaccination strategies, to mitigate risks in this population. Ongoing research is necessary to stay ahead of the evolving viral landscape and emerging variants. Meanwhile, awareness of our current knowledge on how the immune system best combats COVID-19, and how current HM treatments impact immune function must be appreciated, and treatment strategies implemented accordingly to ensure optimal outcomes, not only in achieving disease remission but also in preventing COVID-19 infections.

**Acknowledgements** The authors wish to thank Hennis Tung and Breanna Symmes of GCI Health for writing of the manuscript and Shawna Tan of Medical Writers Asia for literature review.

**Author contributions** The authors confirm their contribution to the paper as follows: HJN, CLW, JYT, HDVP, TQN, and MKA contributed to the conception and design, acquisition, analysis, and interpretation of data; provided critical feedback and inputs for important intellectual content; read and provided final approval of the version to be published. TQN and JYT contributed to the hypothetical case scenario development.

**Data availability** No datasets were generated or analyzed during the current study.

## Declarations

**Conflict of interest** Following the International Committee of Medical Journal Editors' (ICMJE) guidelines, Heng Joo Ng and Chieh Lee Wong report receiving consulting fees and honoraria for lectures and presentations from AstraZeneca. Quang The Nguyen reports receiving consulting fees from AstraZeneca. Phu Huynh Duc Vinh reports receiving consulting fees and honoraria for lectures and presentations from AstraZeneca and Novartis. Maaz Kamal Alata reports receiving honoraria for lectures and presentations for AstraZeneca, Pfizer, and Astellas Pharma. Additionally, he reports receiving meeting attendance support from Astellas Pharma, NewBridge Pharmaceuticals, Merck, and Gilead. Jing Yuan Tan has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.



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