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Original Article

Clinical manifestations and risk factors for COVID-19 and its severity in patients with hematological malignancies

Tzong-Yow Wu [a], Wan-Ting Tsai [a,b], Kai-Hsiang Chen [a,d], Szu-Ting Huang [a,d], Chun-Fu Huang [c], Po-Hsien Kuo [d], Ming-Jui Tsai [c], Wang-Da Liu [a,e,*], Kuan-Yin Lin [a], Yu-Shan Huang [a], Aristine Cheng [a], Pao-Yu Chen [a], Hsin-Yun Sun [a], Huai-Hsuan Huang [a], Tai-Chung Huang [a], Shang-Ju Wu [a], Ming Yao [a], Jann-Tay Wang [a,f], Wang-Huei Sheng [a,g,h], Chien-Ching Hung [a,c,i], Yee-Chun Chen [a,j], Shan-Chwen Chang [a,g]

[a] *Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*
[b] *Department of Internal Medicine, Taipei City Hospital, Zhongxiao Branch, Taipei, Taiwan*
[c] *Department of Internal Medicine, National Taiwan University Hospital Yunlin Branch, Yunlin County, Taiwan*
[d] *Department of Internal Medicine, National Taiwan University Hospital Hsinchu Branch, Hsinchu, Taiwan*
[e] *Department of Medicine, National Taiwan University Cancer Center, Taipei, Taiwan*
[f] *Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Zhunan, Taiwan*
[g] *School of Medicine, National Taiwan University College of Medicine, Taipei, Taiwan*
[h] *Department of Medical Education, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*
[i] *Department of Tropical Medicine and Parasitology, National Taiwan University College of Medicine, Taipei, Taiwan*
[j] *Center of Infection Control, National Taiwan University Hospital, Taipei, Taiwan*

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* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Rd., Taipei City 10002, Taiwan.
E-mail address: b95401043@ntu.edu.tw (W.-D. Liu).

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KEYWORDS
SARS-CoV-2;
Respiratory failure;
Lymphoma;
Stem cell transplant;
Vaccination

Abstract *Background:* Patients with hematological malignancies (HM) were at a high risk of developing severe disease from coronavirus disease 2019 (COVID-19). We aimed to assess the clinical outcome of COVID-19 in hospitalized patients with HM.
Methods: Adult patients with HM who were hospitalized with a laboratory-confirmed COVID-19 between May, 2021 and November, 2022 were retrospectively identified. Primary outcome was respiratory failure requiring mechanical ventilation or mortality within 60 days after hospitalization. We also analyzed associated factors for de-isolation (defined as defervescence with a consecutive serial cycle threshold value $>$ 30) within 28 days.
Results: Of 152 eligible patients, 22 (14.5%) developed respiratory failure or mortality in 60 days. Factors associated with developing respiratory failure that required mechanical ventilation or mortality included receipt of allogeneic hematopoietic stem-cell transplantation (allo-HSCT) (adjusted hazards ratio [aHR], 5.10; 95% confidence interval [CI], 1.64—15.85), type 2 diabetes mellitus (aHR, 2.47; 95% CI, 1.04—5.90), lymphopenia at admission (aHR, 6.85; 95% CI, 2.45—19.15), and receiving $<$2 doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines (aHR, 3.00; 95% CI, 1.19—7.60). Ninety-nine (65.1%) patients were de-isolated in 28 days, against which two hazardous factors were identified: receipt of B-cell depletion therapies within one year prior to COVID-19 (aHR, 0.55, 95% CI, 0.35—0.87) and lymphopenia upon admission (aHR, 0.65; 95% CI, 0.43—1.00).
Conclusion: We found a high rate of respiratory failure and mortality among patients with HM who contracted the SARS-CoV-2. Factors associated with developing respiratory failure or mortality in 60 days included receipt of allo-HSCT, type 2 diabetes mellitus and lymphopenia upon admission. Having received $\geq$2 doses of vaccination conferred protection against clinical progression.
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Introduction

Coronavirus disease 2019 (COVID-19) continues to spread worldwide and has affected 771 million individuals and caused 6.9 million deaths according to the World Health Organization (WHO) as of November 8th, 2023.[1] Previous studies had shown that immunocompromised patients were at risk for developing severe or critical disease, including those with older age, type 2 diabetes mellitus, solid-organ cancer, hematological malignancies (HM), and receipt of solid organ transplantation.[2] Notably, patients with HM were of most concern.[3—5] Previous studies also demonstrated that the risks of developing morbidity and mortality among patients with HM include an active cancer status, receipt of allogeneic hematopoietic stem-cell transplantation (HSCT), concurrent use of anti-cancer therapies and immunosuppressive treatment.[6,7] In addition, patients with HM were found to have suboptimal serological responses to vaccination, which might adversely influence the prognosis when infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[8] The B.1.1.529 (Omicron) variant was considered as a SARS-CoV-2 variant of concern with lower intrinsic virulence and associated with lower morbidity and mortality.[9] However, in a multicentered cohort study enrolling 1548 COVID-19 patients with hematological malignancies, survival was not different between those infected with the B.1.1.529 variant and those infected with the wild-type, the B.1.1.7 (alpha) and the B.1.617.2 (delta) variants.[10] Moreover, prolonged viral shedding was observed in HM patients with COVID-19, especially among those receiving B-cell depletion therapies, including rituximab and obinutuzumab.[11] Timely administrations of nirmatrelvir/ritonavir, remdesivir, or the combined use of remdesivir with convalescent plasma therapy demonstrated a correlation with enhanced clinical outcomes and the prevention of prolonged SARS-CoV-2 infection among HM patients.[12—14] Until now, such analysis focusing Asian patients with HM remains scarce. In this retrospective cohort study, we aimed to assess the clinical outcome of SARS-CoV-2 infection in hospitalized patients with HM and identify the factors associated with disease progression.

Methods

Study population and setting

National Taiwan University Hospital (NTUH) is a 2200-bed university-affiliated hospital which provides both primary and referral care to 90,000 admissions annually. All hospitalized patients who were aged 18 years or older with HM and laboratory confirmed SARS-CoV-2 infection by real-time polymerase chain reaction (RT-PCR) at the NTUH between May, 2021 and November, 2022 were included. We excluded patients who had known past SARS-CoV-2 infections by history taking and search on the reporting system of notifiable disease of Taiwan CDC. Patients who had previous SARS-CoV-2 infections from the record of CDC from December, 2019 before this event were excluded. We did not include patients admitted after 2023 since those with only mild disease were no more required notification, which resulted in difficulties of identifying case systemically, especially for the timing of meeting the criteria of de-isolation.

Medical records for each patient were retrospectively reviewed to obtain age, gender, underlying comorbidities, body-mass index, current status of hematological malignancies, history of anti-cancer treatments, history of SARS-CoV-2 vaccinations, clinical features, hemogram, renal and liver profile, C-reactive protein, serial cycle-threshold values from SARS-CoV-2 PCR and type of antiviral agents prescribed. We used the age-adjusted Charlson comorbidity index (CCI) score to integrate patient age and other underlying comorbidity including type 2 diabetes mellitus, rheumatological diseases, chronic liver diseases, chronic kidney diseases, chronic lung diseases, heart diseases (including coronary artery diseases and heart failure), HIV/AIDS and malignancies into a single index for severity of baselines comorbidities.[15] The COVID-19 disease severity was categorized according to National Institutes of Health (NIH) COVID-19 treatment guidelines.[16] The study was approved by the Research Ethics Committee of the NTUH (NTUH 202207126RIND).

Treatment protocol

All patients were treated according to the latest COVID-19 treatment guidelines issued by Taiwan CDC.[17] Indications for specific anti-viral agents included a three-day remdesivir, a five-day nirmatrelvir plus ritonavir (NMV/r), or a five-day molnupiravir for mild disease; and a five-day remdesivir for moderate or severe disease. No patient received concurrent antiviral treatment combinations. Nevertheless, a transition from nirmatrelvir/ritonavir or molnupiravir to remdesivir, is recommended for patients who progressed to moderate or severe disease. Dexamethasone (6 mg daily up to 10 days, can be stepped down to oral prednisolone in equivalent dose if conditions improve) is recommended for those with severe or critical disease. Tocilizumab or baricitinib is also recommended for patients with severe or critical disease if a CRP level $>$7.5 mg/dL. Corticosteroid and immunosuppressants are employed with caution in patients with HM especially during the early phase of infection to mitigate the risk of co-infections. Those with high procalcitonin level, evidence or overt signs of co-infections, corticosteroid or other immunosuppressants are not routinely administered even if the patients develop oxygen desaturation, especially during the first 7 days of COVID-19. Bamlanivimab plus etesevimab, casirivimab plus imdevimab, and tixagevimab plus cilgavimab are recommended for those with mild disease and at risk for disease progression (old age or comorbidities) who were probably infected by susceptible variants. As anti-viral agents were prescribed during early phase of infection, anti-inflammatory therapies were given later during hyperinflammatory phase according to pathophysiology.[18]

SARS-CoV-2 RT-PCR from nasal swab was tested semi-weekly after hospitalization. Chest radiograph was performed at least weekly. During hospitalization, serum galactomannan antigen (Bio-Rad, Marnes-la-Coquette, France) and cryptococcus antigen (IMMY, Norman, OK, USA) were tested on admission and twice per week as a protocol for hospitalized patients with hematological malignancies. Bacterial and fungal cultures were collected routinely on admission and when the patients were present with suspicious clinical symptoms and signs. The type and site of superinfections were collected. The principles for admission and de-isolation of COVID-19 patients from isolation were according to the regulation by the Central Epidemic Command Center, Taiwan.[17] Patients were de-isolated by fulfilling both of two criteria: (1) defervescence with symptoms improvement; and (2) negative results of two consecutive RT-PCR (undetectable, or a serial cycle threshold value $>$ 30).

Definition

Active disease was defined as receipt of anti-cancer treatment within 1 year and not achieving complete remission more than 2 years.[19] Chronic kidney disease was defined as creatinine clearance rate $<$60 ml/min. Neutropenia was defined as a total neutrophil count $<500 \times 10^9$ cells/L. Lymphopenia was defined as a total lymphocyte count $<500 \times 10^9$ cells/L. B-cell depletion therapies included anti-CD20 agents and bispecific antibodies, including rituximab, obinutuzumab and glofitamab. Respiratory failure was defined as a patient developing oxygen desaturation that required intubation and mechanical ventilation. Secondary bacterial and fungal infections were defined as bacterial and fungal infections 48 h to 28 days from diagnosis of COVID-19, respectively.[20] Secondary fungal infection was judged by experienced infection specialists, based on a comprehensive workup including host factor, clinical presentation and microbiologic evidence according to the EORTC criteria of invasive fungal disease.[21]

Outcome assessment

All of the patients were observed to 60 days after diagnosis of COVID-19. The primary outcome is all-cause mortality or disease progression to respiratory failure in 60 days. The secondary outcomes include: (1) all-cause mortality in 60 days; (2) release from isolation in 28 days; if a patient had not met the criteria to be released from isolation at discharge, 7 days after the discharge day were substituted as the day to be released from isolation; (3) secondary bacterial and secondary fungal infection in 28 days. Considering the clinical manifestation of COVID-19 in HM patients could be atypical and prolonged virus shedding is common, we extended the observation period.[22—24]

Statistical analysis

Categorical variables, such as gender, underlying diseases and antiviral treatment, were compared using Pearson's chi-squared test or Fisher's exact test. Continuous variables including age and Charlson comorbidity index were analyzed using a Mann—Whitney *U* test. We used Cox proportional hazards model to estimate the unadjusted and adjusted hazards ratio (aHRs) for all-caused developing respiratory failure requiring invasive mechanical ventilation or mortality, and fulfilling the criteria of release from isolation. A matching procedure was not performed because it would result in a marked decrease in the number

of included cases. A backward stepwise regression with removal threshold of p = 0.1 was used to select among covariates to be included into the multivariable model. Two distinct models were employed for the multivariable analysis: model A incorporated the administration of <2 doses of vaccination from all vaccine types, while model B specifically integrated the receipt of <2 doses of mRNA vaccines. In addition, anti-SARS-CoV-2 treatments were excluded from the final statistical model in order to avoid the bias by indication. Superinfections were considered as an intermediate variable associated with primary outcome and were excluded from subsequent analysis. A two-tailed p value less than 0.05 was considered statistically significant. All analyses were performed using Stata/SE software, Version 17.0 (https://www.stata.com).

Results

Between May, 2021 and November, 2022, 157 patients with hematological malignancies were admitted to our hospital with the diagnosis of COVID-19, including 90 (57.3%) with mild, 31 (19.7%) with moderate, 31 (19.7%) with severe and 5 (3.2%) with critical disease upon admission. We excluded 5 of the 157 patients who developed respiratory failure that required mechanical ventilation on the same day of admission. Table 1 shows the clinical characteristics of the 152 included patients. The median age was 67 years. Ninety-six (63.2%) and 56 (36.8%) patients had lymphoid and myeloid malignancies, respectively. At the time of the diagnosis of COVID-19, 149 patients (98.0%) had active disease. Fifteen (9.9%) and 11 (7.2%) patients had undergone allogeneic and autologous HSCT, respectively. Among the 15 patients who had undergone allogeneic HSCT (allo-HSCT), 7 (46.7%) had a history of acute graft-versus-host disease (GVHD); 8 (53.3%) and 3 (20.0%) received calcineurin inhibitors-based immunosuppression and corticosteroids at the time of COVID-19 diagnosis, respectively (data not shown).

During a 60-day follow-up period, 22 (14.5%) patients developed respiratory failure that required mechanical ventilation or mortality, which resulted in an incidence rate of 2.4 events per 1000 person-days of follow-up. Factors associated with developing respiratory failure or mortality in 60 days are shown in Table 2. By the employment of model A, factors associated with the occurrence of respiratory failure or mortality in 60 days included allo-HSCT (adjusted hazards ratio [aHR], 5.10; 95% confidence interval [CI], 1.64—15.85), type 2 diabetes mellitus (aHR, 2.47; 95% CI 1.04—5.90), lymphopenia upon admission (aHR, 6.85; 95% CI, 2.45—19.15), and receipt of <2 doses of SARS-CoV-2 vaccine (aHR, 3.00; 95% CI, 1.19—7.60). The Kaplan—Meier survival curve for the occurrence of respiratory failure or mortality in 60 days of patients receiving <2 and ≥ 2 doses of mRNA vaccine are shown in Fig. 1 (log-rank test $p = 0.02$). Among the three patients who received corticosteroids as a treatment for chronic GVHD, one developed respiratory failure on the third day of hospitalization.

Factors associated with all-cause mortality within 60 days are shown in Table 3, which included allo-HSCT (aHR, 9.04; 95% CI, 2.63—31.04), lymphopenia upon admission (aHR, 4.77; 95% CI, 1.45—15.72) and receipt of <2 doses of vaccine (aHR, 3.11; 95% CI, 1.07—9.03). The median time from symptom onset to de-isolation was 18 days (interquartile range [IQR], 13—31). Two hazardous factors against de-isolation within 28 days from admission were identified, including receipt of B-cell depletion therapies within one year prior to SARS-CoV-2 infection (aHR, 0.55; 95% CI, 0.35—0.87) and lymphopenia (aHR, 0.65; 95% CI 0.43—1.00) (Table 4). A sensitivity analysis was performed by excluding 41 (26.1%) patients who had not met the criteria of de-isolation on the day of discharge and the results showed that receipt of B-cell depletion therapies was a hazardous factor against de-isolation in 28 days (aHR, 0.54; 95% CI, 0.30—0.95) (Supplementary Table 1).

Pathogens causing superinfections are listed in Supplemental Table 2. In our cohort, nine (5.9%) and two (1.3%) patients were found to have bacterial and fungal superinfections, respectively. Among patients admitted to the ICU due to respiratory failure, the percentage of secondary fungal infection was 2 out of 22 (9.1%). The median time from the onset of COVID-19 to secondary bacterial or fungal infection was 5 days (IQR, 3—11). The most common site of bacterial infection was bloodstream, followed by lower respiratory tract and urinary tract. The most common causative pathogens were *Escherichia coli* and *Klebsiella pneumoniae*. Two patients developed secondary fungal infections, including one with *Trichosporon asahii* pneumonia 4 days after COVID-19, and the other with probable COVID-19-related pulmonary aspergillosis (CAPA) 18 days after COVID-19 diagnosis. We failed to identify any factors associated with bacterial or fungal superinfections in the statistical model, probably related to small case numbers (data not shown).

Discussion

In the present study, we found that receipt of allo-HSCT, lymphopenia upon admission, type 2 diabetes mellitus, and receiving ≤1 dose SARS-CoV-2 vaccine were factors associated with developing respiratory failure or death in 60 days. Receipt of B-cell depletion therapies within one year and lymphopenia were associated with delayed de-isolation.

Previous studies demonstrated that patients with hematological malignancies have a worse outcome when infected with SARS-CoV-2, especially among those with elder age, refractory disease, lymphopenia and other comorbidities.[2,6,10,25] The all-cause mortality rate was 11.5% in our study. During the same period in Taiwan, that in the general population was 0.17% only (14,322 deaths out of 8,312,245 COVID-19 confirmed cases according to data from Taiwan Centers for Disease Control [CDC]).[26] Lymphopenia is a well-known factor associated with poor outcome in other respiratory disease such as influenza.[27—29] In patients with SARS-CoV-2 infection, profound lymphopenia was associated with dampened lymphocyte production, dysregulation of lymphocyte subsets, lower levels of anti-SARS-CoV-2 proteins and tissue redistribution, consequently leading to higher risk of respiratory failure, secondary infection and mortality.[30—33] In addition, our study highlighted the status of allo-HSCT was associated with high risk developing respiratory failure or mortality. Busca et al. demonstrated that development of COVID-19 within 12

Table 1 Baseline characteristics of the included patients with hematological malignancies.

Characteristic	Total (n = 152) (%)	Respiratory failure or death in 60 days (n = 22) (%)	No respiratory failure or death in 60 days (n = 130) (%)	*p* value
Demographics				
Male	88 (57.9)	12 (54.6)	76 (58.5)	0.73
Age, year (IQR)	67 (56–77)	66 (57–72)	67 (56–77)	0.88
Hematological malignancy				
Active disease	149 (98.0)	21 (95.5)	128 (98.5)	0.35
Categories				0.96
Lymphoid malignancies	96 (63.2)	14 (63.6)	82 (63.1)	
Myeloid malignancies	56 (36.8)	8 (36.4)	48 (36.9)	
Types				0.22
Non-Hodgkin lymphoma	71 (46.7)	11 (50.0)	60 (46.2)	
Other lymphoid malignancies	25 (16.5)	3 (13.6)	22 (16.9)	
Acute myeloid leukemia	30 (19.7)	7 (31.8)	23 (17.7)	
Other myeloid malignancies	26 (17.1)	1 (4.6)	25 (19.2)	
Clinical features				
Age-adjusted Charlson comorbidity index (IQR)	5 (3–7)	5 (4–6)	5 (3–7)	0.66
Age-adjusted Charlson comorbidity index >4	84 (55.3)	14 (63.6)	70 (53.9)	0.39
BMI >30 kg/m^2	10 (6.6)	1 (4.6)	9 (6.9)	0.68
Type 2 diabetes mellitus	41 (27.0)	9 (40.9)	32 (24.6)	0.11
Cirrhosis	14 (9.2)	3 (13.6)	11 (8.5)	0.44
CAD or heart failure	16 (10.5)	3 (13.6)	13 (10.0)	0.61
Chronic kidney disease	74 (48.9)	13 (59.1)	61 (46.9)	0.29
Neutropenia	21 (13.8)	4 (18.2)	17 (13.1)	0.52
Lymphopenia	56 (36.8)	16 (72.7)	40 (30.8)	**<0.01**
Receipt of HSCT				
Allogeneic HSCT	15 (9.9)	5 (22.7)	10 (7.7)	**0.03**
Autologous HSCT	11 (7.2)	0 (0.0)	11 (8.5)	0.16
Receipt of cancer treatment in recent 1 year				
Chemotherapy	92 (60.6)	14 (63.6)	78 (60.0)	0.75
Demethylating agents	11 (7.2)	2 (9.1)	9 (6.9)	0.72
CAR-T	1 (0.66)	0 (0.0)	1 (0.77)	1.00
B-cell depletion therapies[a]	55 (36.2)	9 (36.4)	47 (36.2)	0.99
Supportive measures only	5 (3.3)	0 (0.0)	5 (3.9)	0.35
Vaccination of all vaccine types				
≥2 doses	97 (63.4)	7 (30.4)	90 (69.2)	**<0.01**
≥3 doses	68 (44.7)	6 (27.3)	62 (47.7)	0.08
No vaccination	36 (23.7)	12 (54.6)	24 (18.5)	**<0.01**
Vaccination of mRNA vaccines				
≥2 doses	63 (41.5)	4 (18.2)	59 (45.4)	**0.02**
≥3 doses	36 (23.7)	2 (9.1)	34 (26.2)	0.08
COVID-19 severity on admission				
Mild	90 (59.2)	6 (27.3)	84 (64.6)	**0.01**
Moderate	31 (20.4)	3 (13.0)	28 (21.5)	0.40
Severe	31 (20.4)	13 (56.5)	18 (13.9)	**<0.01**
Receipt of COVID-19 treatment				
Nirmatrelvir/ritonavir	53 (34.9)	4 (18.2)	49 (37.7)	0.06
Molnupiravir	40 (26.3)	8 (36.4)	32 (24.6)	0.25
Remdesivir	95 (62.5)	19 (86.4)	76 (58.5)	**0.01**
Monoclonal antibodies[b]	16 (10.5)	3 (13.6)	13 (10.0)	0.61
Corticosteroid	32 (21.1)	12 (54.6)	20 (15.4)	**<0.01**
Tocilizumab	5 (3.3)	3 (13.6)	2 (1.5)	**<0.01**
Baricitinib	2 (1.3)	1 (4.6)	1 (0.8)	0.15
Release from isolation in 28 days	99 (65.1)	6 (27.3)	93 (71.5)	**<0.01**
Superinfection				
Secondary bacterial/fungal infections	11 (7.2)	6 (27.3)	5 (3.9)	**<0.01**
Secondary bacterial infections	9 (5.9)	4 (18.2)	5 (3.9)	**<0.01**
Secondary fungal infections	2 (1.3)	2 (9.1)	0 (0.0)	**0.02**

[a] B-cell depletion therapies were as followed: rituximab (n = 45), obinutuzumab (n = 4), the bispecific antibody glofitamab (n = 4), the anti-CD20 trial medication CHO−H01 (n = 2).
[b] Monoclonal antibodies were as followed: bamlanivimab plus etesevimab (n = 2), tixagevimab plus cilgavimab (n = 14).
Abbreviations. IQR, interquartile range; CAD, coronary artery disease; HSCT, hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor T-cell therapy.

months of allo-HSCT was associated with higher mortality among patients with hematological malignancies.[7] Our study did not show an association between the time from HSCT to COVID-19 diagnosis and mortality. Presumably, hospitalized patients had higher clinical complexities, and HSCT over 12 months remained to be high risk among this population.

In our study, having received 2 or more doses of SARS-CoV-2 vaccines are associated with lower risk of developing respiratory failure or mortality, regardless of the type of vaccination. The U.S CDC had announced that those with immunocompromised status, such as hematological malignancy or HSCT were prioritized in the COVID-19 vaccination programs.[34] However, suboptimal serological responses after a two-dose primary vaccination were observed among those with hematological malignancies, especially among those with chronic lymphoblastic leukemia (CLL), non-Hodgkin's lymphoma (NHL) and receiving B-cell depletion therapies.[35−38] Since lower serological responses might be associated with increasing breakthrough infection and more severe disease, an additional third dose or a booster dose was recommended for all patients with hematological malignancies.[6,39,40] Until now, there has been limited data available on real-world COVID-19

Table 2 Factors associated with developing respiratory failure requiring mechanical ventilation or death within 60 days after admission.

	Univariable		Multivariable (model A)[a]		Multivariable (model B)[b]	
	HR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*
Male	0.85 (0.37−1.96)	0.70	—	—	—	—
Age, per 1 year increase	1.00 (0.98−1.03)	0.81	—	—	—	—
Active disease	0.32 (0.04−2.38)	0.27	—	—	—	—
HM categories						
Myeloid malignancies	**Ref**	—	—	—	—	—
Lymphoid malignancies	0.98 (0.41−2.34)	0.97	—	—	—	—
HM types						
Other myeloid malignancies	**Ref**	—	—	—	—	—
Acute myeloid leukemia	6.79 (0.83−55.20)	0.07	—	—	—	—
Non-Hodgkin lymphoma	4.11 (0.53−31.82)	0.18	—	—	—	—
Other lymphoid malignancies	3.20 (0.33−30.80)	0.31	—	—	—	—
Anti-cancer treatment						
Allogeneic HSCT	3.13 (1.15−8.49)	**0.03**	5.10 (1.64−15.85)	**0.01**	6.26 (2.05−19.10)	**<0.01**
Autologous HSCT	—	—	—	—	—	—
B-cell depletion therapies	0.97 (0.41−2.32)	0.95	—	—	—	—
Clinical features						
Age-adjusted Charlson comorbidity index >4	1.47 (0.62−3.51)	0.38	—	—	—	—
BMI >30 kg/m^2	0.66 (0.09−4.88)	0.68	—	—	—	—
Type 2 diabetes mellitus	2.03 (0.87−4.75)	0.10	2.47 (1.04−5.90)	**0.04**	2.65 (1.11−6.32)	**0.03**
Cirrhosis	1.66 (0.49−5.62)	0.41	—	—	—	—
CAD or heart failure	1.48 (0.44−5.02)	0.53	—	—	—	—
Chronic kidney disease	1.61 (0.69−3.77)	0.27	—	—	—	—
Neutropenia	1.42 (0.48−4.20)	0.52	—	—	—	—
Lymphopenia	5.09 (1.99−13.01)	**<0.01**	6.85 (2.45−19.15)	**<0.01**	7.22 (2.59−20.16)	**<0.01**
Vaccination of all vaccine types						
<2 doses vs ≥ 2 doses	4.11 (1.67−10.08)	**<0.01**	3.00 (1.19−7.60)	**0.02**	—	—
<3 doses vs ≥ 3 doses	2.25 (0.88−5.76)	0.09	—	—	—	—
Vaccination of mRNA vaccines						
<2 doses vs ≥ 2 dose	3.45 (1.17−10.21)	**0.03**	—	—	3.00 (1.00−8.99)	**0.05**
<3 doses vs ≥ 3 dose	3.35 (0.78−14.35)	0.10	—	—	—	—

[a] Model A included <2 doses of vaccination of all vaccine types for multivariable analysis. Acute myeloid leukemia is removed by backward stepwise regression.
[b] Model B included <2 doses of RNA vaccine for multivariable analysis. Acute myeloid leukemia is removed by backward stepwise regression.
Abbreviations. HR, hazard ratio; aHR, adjusted hazard ratio; IQR, interquartile range; HM, hematological; HSCT, hematopoietic stem cell transplantation.

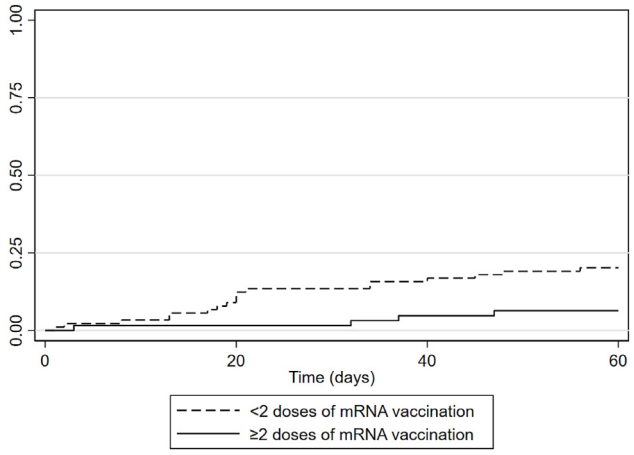

Figure 1. Respiratory failure or death in 60 days among hospitalized patients diagnosed with hematological malignancies who received varied vaccination doses (Log-rank test $p = 0.02$).

vaccination within large cohort studies. Previous research has suggested that although booster vaccinations can boost SARS-CoV-2 antibody levels; however, breakthrough infections have remained common, with a predominantly mild clinical course.[41,42] Our study further demonstrated a tendency for better clinical outcome in patients with COVID-19 who had received at least 2 doses or 3 doses of vaccination, respectively. However, the latter failed to show statistical significance, probably due to small sample size. Although mRNA vaccines have been shown to be associated with higher antibody and T cell responses compared to non-mRNA vaccines, studies on the benefit of mRNA vaccine in patients with hematological malignancies have been limited. In our study, the receipt of vaccination of mRNA vaccines and all vaccine types are both associated with a lower risk of respiratory failure and death using two models in multivariable analysis. Whether non-mRNA vaccination is probably similarly effective in preventing worse clinical outcome in patients with hematological malignancies warrant more investigations.

Table 3 Factors associated with all-cause mortality within 60 days after admission.

	Univariable		Multivariable	
	HR (95% CI)	*P*	aHR (95% CI)	*P*
Male	1.01 (0.39–2.66)	0.98	–	–
Age, per 1 year increase	0.99 (0.97–1.02)	0.72	–	–
Active disease	0.23 (0.03–1.74)	0.15	–	–
HM categories				
Myeloid malignancies	Reference	–	–	–
Lymphoid malignancies	1.10 (0.41–2.96)	0.86	–	–
HM types				
Other myeloid malignancies	Reference	–	–	–
Acute myeloid leukemia	4.87 (0.59–40.49)	0.14	–	–
Non-Hodgkin lymphoma	3.49 (0.45–27.26)	0.23	–	–
Other lymphoid malignancies	–	–	–	–
Anti-cancer treatment				
Allogeneic HSCT	5.03 (1.86–13.63)	**<0.01**	9.04 (2.63–31.04)	**<0.01**
Autologous HSCT	–	–	–	–
B-cell depletion therapies	1.25 (0.47–3.27)	0.66	–	–
Clinical features				
Age-adjusted Charlson comorbidity index >4	2.00 (0.71–5.69)	0.19	–	–
BMI >30 kg/m^2	–	–	–	–
Diabetes mellitus	2.41 (0.93–6.24)	0.07	2.47 (0.94–6.48)	0.07
Cirrhosis	2.43 (0.70–8.45)	0.16	–	–
CAD or heart failure	–	–	–	–
Chronic kidney disease	1.22 (0.47–3.17)	0.68	–	–
Neutropenia	1.43 (0.41–4.97)	0.58	–	–
Lymphopenia	2.62 (1.00–6.88)	0.05	4.77 (1.45–15.72)	**0.01**
Vaccination of all vaccine types				
<2 doses vs ≥ 2 doses	4.49 (1.58–12.76)	**<0.01**	3.11 (1.07–9.03)	**0.04**
<3 doses vs ≥ 3 doses	3.76 (1.08–13.08)	**0.04**	–	–
Vaccination of mRNA vaccines				
<2 doses vs ≥ 2 doses	2.38 (0.78–7.30)	0.13	–	–
<3 doses vs ≥ 3 doses	2.33 (0.53–10.20)	0.26	–	–

Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio; IQR, interquartile range; HM, hematological; HSCT, hematopoietic stem cell transplantation.

Table 4 Factors associated with successfully achieving the criteria of being released from isolation in 28 days after admission.

	Univariable		Multivariable[a]	
	HR (95% CI)	*P*	aHR (95% CI)	*P*
Male	0.90 (0.61—1.34)	0.62	—	—
Age, per 1 year increase	1.00 (0.99—1.01)	0.73	—	—
Active disease	0.59 (0.14—2.39)	0.46	—	—
HM categories				
Myeloid malignancies	Reference	—	—	—
Lymphoid malignancies	0.76 (0.51—1.13)	0.18	—	—
HM types				
Other myeloid malignancies	Reference	—	—	—
Acute myeloid leukemia	0.59 (0.32—1.07)	0.08	—	—
Non-Hodgkin lymphoma	0.51 (0.30—0.85)	**0.01**	—	—
Other lymphoid malignancies	0.79 (0.43—1.48)	0.47	—	—
Anti-cancer treatment				
Allogeneic HSCT	0.78 (0.38—1.61)	0.51	—	—
Autologous HSCT	0.81 (0.35—1.84)	0.61	—	—
B-cell depletion therapies	0.54 (0.35—0.85)	**<0.01**	0.55 (0.35—0.87)	**0.01**
Clinical features				
Age-adjusted Charlson comorbidity index >4	1.11 (0.75—1.65)	0.60	—	—
BMI >30 kg/m^2	1.24 (0.60—2.55)	0.56	—	—
Type 2 diabetes mellitus	0.96 (0.61—1.52)	0.87	—	—
Cirrhosis	1.10 (0.51—2.38)	0.80	—	—
CAD or heart failure	0.70 (0.36—1.34)	0.28	—	—
Chronic kidney disease	0.98 (0.66—1.45)	0.93	—	—
Neutropenia	0.82 (0.45—1.50)	0.52	—	—
Lymphopenia	0.63 (0.41—0.97)	**0.03**	0.65 (0.43—1.00	**0.05**
Vaccination of all vaccine types				
<2 doses vs ≥ 2 doses	0.79 (0.52—1.21)	0.28	—	—
<3 doses vs ≥ 3 doses	0.73 (0.49—1.08)	0.12	—	—
Vaccination of mRNA vaccines				
<2 doses vs ≥ 2 doses	0.93 (0.63—1.37)	0.70	—	—
<3 doses vs ≥ 3 doses	0.73 (1.09—0.98)	0.12	—	—

[a] Non-Hodgkin lymphoma is removed by backward stepwise regression.
Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio; IQR, interquartile range; HM, hematological; HSCT, hematopoietic stem cell transplantation.

Prolonged viral shedding up to several months is common in patients with hematological malignancies.[43,44] However, information on associated factors of prolonged shedding is limited. Previous studies showed that older age, relapsed/refractory disease status, B-cell depletion therapy, HSCT and lymphopenia were factors associated with prolonged viral shedding.[11] In our study, delayed de-isolation was associated with B-cell depletion therapy and lymphopenia in multivariable analysis. Kim et al. showed that patients with lymphopenia were likely to be immunocompromised and have a lower anti-SARS-CoV-2 antibody level.[45] In addition, initial lymphopenia was demonstrated to be associated with more SARS-CoV-2 viral rebound.[46] Receipt of active immunosuppressive treatment was also associated with increased odds of viral rebound.[47] Of the immunosuppressive treatments, B-cell depletion therapy with medications such as rituximab and obinutuzumab is one of the common therapeutic approaches in B cell malignancies. Several case series had shown that B-cell depletion therapy may cause persistent/relapsing SARS-CoV-2 infections in patients with hematological malignancies.[48,49] In addition to experiencing an extended course of infection, patients who received targeted drugs including Bruton-kinase inhibitors and anti-CD20 therapies may exhibit elevated disease severity and mortality associative with COVID-19.[50] Preventive and therapeutic measures including vaccination and monoclonal antibodies active against the predominant SARS-CoV-2 variants could be effective to reduce persistent/relapsing infection in this population.[49]

In our cohort, 9 (5.7%) patients developed secondary bacterial infections over a 28-day observation period. Previous studies have demonstrated an incidence of secondary infection of 3.8—5% among hematologic patients with SARS-CoV-2 infection.[20,51] In our study, secondary fungal infections developed in 2 of 152 patients (1.3%) during the 28-day observation period. Both patients were intubated and admitted to ICU within 20 days after the diagnosis of COVID-19, and one patient died on day 47 after COVID-19 diagnosis. Previous studies on secondary fungal infection among severe/critical participants, i.e. mechanically ventilated, acute respiratory distress syndrome or ICU admission, showed a 30-day cumulative incidence of 8.5%—15%, and a high mortality rate between 43% and 62%.[52,53] While the low incidence of secondary fungal infection in our study

could be directly caused by the inclusion of non-ICU patients, it could also be the result of our prudent use of corticosteroids in patients with severe or critical disease; among the 36 patients who required supplemental oxygen at baseline, only 25 received antiinflammatory therapy (16 receiving corticosteroids only, 5 receiving corticosteroids and tocilizumab, 3 receiving corticosteroids and baricitinib, and 1 received tocilizumab only). Considering co-infection and superinfection remains a common clinical scenario among HM patients with COVID-19, the use of corticosteroid should be cautious as previous studies demonstrated potential negative impact, including infection and prolonged viral shedding.[54—56] Since increased risk for fungal infection was found for both patients with HM and COVID-19. Regular and active surveillance is warranted for timely diagnosis and improving clinical outcome.

A strength of the current study is that all participants were treated according to national treatment guidelines.[17] There are several limitations of the current study, however. First, this was a single center observational study with a small sample size. Second, the subvariant strains of SARS-CoV-2 was not evaluated, making it difficult to differentiate between relapsed infection and reinfection and to identify possible antiviral resistance. SARS-CoV-2 Ct value does not necessarily equal to viral viability; however, a positive correlation has been established by previous studies.[57] Furthermore, we did not evaluate the impact of dexamethasone, tocilizumab and baricitinib for COVID-19 on primary and secondary outcomes, because confounding by indication may occur in cohort studies. Last, we did not discuss the differences between different brands/dose of COVID-19 vaccine, and the interval between the second and third dose of vaccination was not evaluated.

Patients with hematological malignancies had a higher risk of COVID-19 clinical progression. While allo-HSCT, lymphopenia and type 2 diabetes mellitus were associated with more respiratory failure or death, receiving $\geq$2 doses of SARS-CoV-2 vaccines was associated with less clinical progression. Receipt of B-cell depletion therapy was associated with prolonged isolation. Further investigation into the relationship between B-cell depletion therapy and prolonged viral shedding is warranted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.03.001.