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**Title:** COVID-19 in Vaccinated Versus Unvaccinated Hematologic Malignancy Patients

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**Abstract**

The effect of vaccination on severity of subsequent COVID-19 in patients with hematologic malignancies (HM) is unknown. In this single-center retrospective cohort study, we found no

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difference in severity of COVID-19 disease in vaccinated (n=16) versus unvaccinated (n=54) HM patients using an adjusted multiple logistic regression model. Recent anti-B-cell therapy was associated with more severe illness.

### **List of Abbreviations**

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T (cell); CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; DM, diabetes mellitus; HM, hematologic malignancy; HSCT, hematopoietic stem cell transplant; HTN, hypertension; IQR, interquartile range; mRNA, messenger ribonucleic acid; O<sub>2</sub>, oxygen.

### **Introduction**

Patients with hematologic malignancy (HM) and SARS-CoV-2 infection experience poor outcomes, with increased rates of severe disease and reported mortality ranging from 15-39%<sup>1-6</sup>. For immunocompetent patients, a primary vaccine series, consisting of two mRNA vaccine doses or one Johnson & Johnson vaccine dose, results in markedly attenuated disease severity compared to those who have not been vaccinated<sup>7</sup>. Given the increased

risk of severe illness in HM patients, professional society guidelines have recommended that they be prioritized for vaccination<sup>8</sup>. However, prior studies have found that HM patients mount a decreased humoral response to COVID-19 vaccination<sup>9–11</sup>, and their degree of protection from clinical disease after vaccination is not well understood. The available literature suggests that HM patients who have been vaccinated can still experience severe disease<sup>12</sup>, including death<sup>10,13</sup>. However, few studies published to date have systematically examined clinical outcomes in vaccinated HM patients who develop COVID-19, and the effect of vaccination on COVID-19 severity in this population is unknown.

## **Methods**

We performed a retrospective multiple cohort study comparing previously vaccinated to unvaccinated HM patients with COVID-19. All adult HM patients (age  $\geq 18$  years) who received inpatient or outpatient care at the University of California, San Francisco (UCSF), and who were diagnosed with COVID-19 by SARS-CoV-2 RT-PCR between December 1, 2020 and August 15, 2021, were included in the study. Subjects were identified via standard reporting to UCSF HM and Infection Control programs; these programs maintain a running list of all COVID-19 positive HM patients, both inpatients and outpatients, including those

who were tested at other facilities. Vaccinated patients were defined as those who had received at least one dose of COVID-19 vaccine prior to diagnosis; “fully vaccinated” patients had first positive COVID-19 test at least two weeks after their second mRNA vaccine dose or their only adenovirus vector (Johnson & Johnson) vaccine dose. The HM program’s vaccination guidance during the study period was that all patients should be vaccinated, with the exception of patients who were within the period from four weeks before to three months after hematopoietic stem cell transplant (HSCT) or chimeric antigen receptor T-cell (CAR-T) therapy.

Data extracted from the electronic medical record included demographics (age, gender, race, Latinx ethnicity), comorbidities known to be risk factors for COVID-19 disease severity (diabetes, hypertension, obesity), HM disease and treatments (subtype, whether in remission, whether receiving active chemotherapy, history of allogeneic or autologous HSCT, receipt of anti-B-cell therapy within the last 18 months), SARS-CoV-2 vaccine dates and characteristics, and COVID-19 disease characteristics and treatments. “Active chemotherapy” was defined as receipt of chemotherapy within three months prior to first positive SARS-CoV-2 test. SARS-CoV-2 variant status, as determined by whole-genome sequencing as previously described<sup>14</sup>, was collected when available on PCR tests run at our



center. Primary outcomes were hospital admission for COVID-19 and COVID-19 disease severity as defined by the World Health Organization [WHO] Ordinal Scale<sup>15</sup>.

Baseline characteristics were compared between the two groups using Fisher's exact test (categorical variables) or the Kruskal-Wallis test (continuous variables). Odds ratios (ORs) were calculated using univariate logistic regression. Multiple logistic regression was then performed to control for baseline differences between the groups and likely confounders; covariates included in the model were age, diabetes mellitus, history of chimeric antigen receptor T-cell (CAR-T) therapy, active chemotherapy, anti-B-cell therapy within the prior 18 months, and high-risk neutropenia (defined as absolute neutrophil count  $<500$  cells/ $m^3$  for  $>7$  consecutive days in the prior three months). Monoclonal antibody receipt was not included as a predictor variable in the main logistic regression analyses because eligibility for monoclonal antibodies was partly dependent on the outcomes (patients who did not become symptomatic would not qualify, nor would patients who were ill enough to require hospitalization at symptom onset). All statistical analysis was conducted using Stata (15.1, StataCorp LLC, College Station, TX). The study was approved by the UCSF institutional review board.

## **Results**

A total of 70 HM patients with COVID-19 were included in the analysis. The cohort was 47.1% male, with a median age of 42.3 years (IQR: 33.5, 60.9). The racial and ethnic make-up of the participants was 44.3% white, 8.6% Asian, 7.2% Black, and 40.0% other or unknown; 37.1% identified as Latinx. The hematologic malignancies represented included multiple myeloma (30.0%), diffuse large B-cell lymphoma (11.4%), chronic myelogenous leukemia (11.4%), acute myeloid leukemia (8.6%), acute lymphocytic leukemia (8.6%), and other (30.0%). Forty percent had a history of HSCT, of which half were allogeneic and half autologous. A total of 61.4% were receiving active chemotherapy; 5.7% had received CAR-T cell therapy; and 21.7% had received anti-B-cell therapy within the 18 months prior to their positive COVID-19 test.

Among the cohort, 83.1% were symptomatic at the time of their positive COVID-19 test, and 91.4% developed symptoms at some point in their course of illness. The rate of admission for COVID-19 was 25.7%; just 2.9% required mechanical ventilation, and 2.9% died due to COVID-19. The median WHO ordinal severity score was 2 (IQR: 2, 3), corresponding to limitation of activities without need for hospitalization. The treatments received were

monoclonal antibody treatment (35.3%); remdesivir (30.0%); convalescent plasma (14.5%); dexamethasone (14.3%); and tocilizumab (1.4%).

Of the 70 included subjects, 16 were classified as having breakthrough COVID-19 (**Table 1**). All received mRNA vaccine; 15 were fully vaccinated, and one was partially vaccinated. They developed breakthrough infection at a median of 96 days (IQR: 74.5, 126.5) after their last vaccine dose. Of note, because the study period preceded the recommendation that immunocompromised patients receive a three-dose primary series, no patient received a third dose. Vaccinated HM patients were significantly younger, but otherwise without significant differences in demographics, comorbidities, or HM disease characteristics and treatments (**Table 1**). Vaccinated patients were more likely to develop COVID-19 after the delta variant became predominant in June 2021<sup>16</sup> (**Figure 1**), and more likely to receive monoclonal antibody therapy (**Table 1**). Among the vaccinated patients, COVID-19 anti-spike IgG antibodies were available for five either prior to or within three days of initial positive test; 40% were positive. Samples from 11 patients underwent whole-genome sequencing for SARS-CoV-2 virus variant status, and two of three vaccinated patients and one of eight unvaccinated patients had the delta variant.

On univariate logistic regression, diabetes, high-risk neutropenia, receipt of CAR T-cell therapy, and receipt of anti-B-cell therapy were associated with increased odds of COVID-19 admission and increased COVID-19 severity, whereas receipt of active chemotherapy was associated with decreased odds of these outcomes (**Table S1**). On multiple logistic regression analyses adjusting for age and above variables, there was no significant difference between the vaccinated and unvaccinated HM patients with regards to COVID-19 outcomes: adjusted OR for hospitalization for COVID-19 was 0.85 (95% confidence interval, 0.14-5.14,  $p=0.86$ ), and for COVID-19 severity by ordinal scale, 1.01 (0.28-3.73,  $p=0.98$ ). However, receipt of anti-B-cell therapy in the 18 months prior to COVID-19 diagnosis was associated with increased odds of admission for COVID-19 within the cohort as a whole (OR 9.05, 95%CI 1.73-47.26,  $p=0.01$ ) and with COVID-19 disease severity (OR 5.28, 95%CI 1.34-20.73,  $p=0.02$ ).

Monoclonal antibody treatment was associated with decreased risk of COVID-19 hospitalization (OR 0.08, 95% CI 0.01-0.62,  $p=0.02$ ) and decreased COVID-19 severity (OR 0.32, 95% CI 0.11-0.96,  $p=0.04$ ) in univariate regressions. Because more vaccinated patients received monoclonal antibodies, a sensitivity analysis including monoclonal antibody receipt in the multivariate regression model was performed. This continued to show no significant difference in vaccinated versus unvaccinated patients for either outcome.

## Discussion

In this single-center cohort, prior vaccination did not appear to be associated with need for hospital admission or with severity of disease in HM patients with COVID-19. This was true despite a significantly higher rate of monoclonal antibody treatment in the vaccinated group, which might have been expected to bias the results toward better outcomes among vaccinated patients. Although multiple prior studies have raised the concern that HM patients mount a decreased humoral response to vaccination<sup>9-12</sup>, few studies published to date have systematically examined the effect of vaccination on subsequent COVID-19 infection severity in this population. Our findings suggest that a two-dose vaccination series may not attenuate disease severity in HM patients who develop symptomatic breakthrough infection. This result is concordant with a recently-published retrospective study that found that vaccination against COVID-19 did not protect against hospitalization or 30-day mortality among patients with cancer, including a small number of HM patients<sup>17</sup>. Of note, since the study period, vaccine guidance in the United States has been updated to include the recommendation that immunocompromised patients receive a three-dose primary vaccine series. No patients in the study received a third dose, and it is unknown whether patients

who develop breakthrough infection after a three-dose series might have less severe disease. Further study in this area is urgently needed.

We did find that prior B-cell depleting therapy was a risk factor for COVID-19 admission and for increased severity of disease. Previous reports have suggested that anti-CD20 therapy is a risk factor for prolonged SARS-CoV-2 viral replication and lack of serologic response to infection<sup>18</sup>, as well as a risk factor for severe COVID-19 outcomes. In a multicenter study of 111 patients with lymphoma who required admission for COVID-19, receipt of anti-CD20 therapy was associated with a significant increase in length of stay and mortality<sup>19</sup>. Poor humoral response to COVID-19 vaccines after B-cell-depleting therapy has also been reported<sup>12</sup>. For example, in a study of 96 patients who had received B-cell-depleting therapy for a variety of indications, 49% had detectable anti-spike IgG after vaccination, compared with 100% of immunocompetent controls<sup>20</sup>; in a cohort of 1303 HM patients, anti-CD20 therapy was associated with a significant decrease in quantitative anti-spike IgG levels, with a median level of 17 AU/mL, below the threshold for positivity<sup>10</sup>. While poor humoral response to vaccine might be expected to correspond to more severe infections after vaccination, this has not yet been shown. In our study, none of the vaccinated patients who had received B-cell depleting therapy had anti-spike IgG checked prior to infection onset.

Immune response, including presence of neutralizing antibodies among vaccinated HM patients who develop COVID-19, is an area for future study.

Of note, the outcomes in our cohort overall were significantly better than those reported in the literature for patients with hematologic malignancy; 26% required hospitalization for COVID-19, and the rate of both mechanical ventilation and COVID-19-related mortality was just 3%. This may be a result of the study setting in a center that was adequately resourced throughout the pandemic, or could be because our case sampling included both inpatients and outpatients. The largest studies on this topic have included predominantly hospitalized patients<sup>2,3</sup>; for example, in Vijenthira and colleagues' pooled analysis of outcomes in 3377 HM patients, which reported a 34% overall mortality rate, 77% of patients were hospitalized<sup>1</sup>. Regardless, the small number of severe outcomes likely decreased the study's power to detect effect of vaccination, and larger studies would be needed in order to conclude that vaccination does not attenuate disease severity in this population.

Besides its small size, the study has several limitations. First, variant status as determined by whole-genome sequencing was available for only 16% of the cohort. However, 75% of the infections in vaccinated patients occurred after mid-June 2021, compared with only 6%

of infections in unvaccinated patients, so it is highly likely that the vaccinated group contained a higher proportion of infections with the delta variant. As the delta variant has been associated with worse outcomes<sup>21</sup>, this may have decreased the apparent effect of vaccination. Second, as few serologies were available prior to infection onset, we were unable to evaluate the effect of humoral response to vaccine. Third, there may have been unmeasured differences between the vaccinated and unvaccinated patients; for example, vaccinated patients may have had greater proximity or access to care (and we hypothesize that this is the reason for the higher rate of monoclonal antibody treatment in the vaccinated group). While we attempted to ameliorate this issue by including patients going back to December 2020, prior to widespread vaccine availability, it is possible that differences remained, and this could have affected the results. Fourth, as previously mentioned, no patients in the cohort received a third vaccine dose, and conclusions cannot be drawn about severity of breakthrough infections in patients who have received a three-dose series. Finally, most patients in the cohort were tested because of symptoms, and therefore any effect of vaccine in preventing development of symptoms or in preventing infection entirely would not have been detected by the study.

In sum, we found no association between prior vaccination and COVID-19 disease severity in our patients with hematologic malignancies, and only receipt of recent anti-B-cell therapy



was significantly associated with increased severity of disease in a multivariate regression model. Additional investigation is needed to better understand the immunologic and behavioral basis for these findings. Even among unvaccinated patients, we found a lower rate of severe outcomes, including need for mechanical ventilation and mortality, than has previously been reported for this population. Further study is urgently needed to better characterize the immune response to COVID-19 vaccination and clinical outcomes of breakthrough COVID-19 in the HM population, particularly in light of newer recommendations that HM patients receive a three-dose primary vaccine series. These populations may benefit from additional strategies for prevention including passive immunotherapy.

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**Potential Conflicts of Interest:** C.Y.C. is the director of the UCSF-Abbott Viral Diagnostics and Discovery Center and receives research support from Abbott Laboratories, Inc. The other authors declare no potential conflicts of interest.

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## **TABLES**

**Table 1.** Selected baseline and COVID-19 disease characteristics of vaccinated versus non-vaccinated patients

	<b>Vaccinated (n=16)</b>	<b>Unvaccinated (n=54)</b>	<b>P-value</b>
<b>Baseline Characteristics</b>			
Age, median (IQR)	35.5 (27.5, 44.0)	45.4 (36.0, 63.0)	<b>0.01</b>
Male, n (%)	8 (50.0)	25 (46.3)	1.00
Race, n (%)			
White	9 (56.3)	22 (40.7)	0.39
Black	0 (0.0)	5 (9.3)	0.58
Asian	2 (12.5)	4 (7.4)	0.61
American Indian/Alaska Native	0 (0.0)	1 (1.9)	1.00
Other	6 (37.5)	21 (38.9)	1.00
Unknown	0 (0.0)	1 (1.9)	1.00
Latinx ethnicity, n (%)	5 (31.2)	21 (38.9)	0.77

DM, n (%)	3 (18.5)	8 (14.8)	0.71
HTN, n (%)	5 (31.2)	19 (35.2)	1.00
Obesity, n (%)	4 (25.0)	21 (38.9)	0.38
Malignancy, n (%)			
ALL	1 (6.3)	5 (9.3)	0.32
AML	0 (0.0)	6 (11.1)	1.00
CML	0 (0.0)	8 (14.8)	0.18
DLBCL	4 (25.0)	4 (7.4)	0.07
Multiple myeloma	3 (18.8)	18 (33.3)	0.36
Other	8 (50.0)	13 (24.1)	0.06
Active chemotherapy, n (%)	9 (56.3)	34 (63.0)	0.77
Anti B-cell therapy <sup>a</sup> , n (%)	6 (37.5)	9 (17.0)	0.10
HSCT, n (%)	4 (25.0)	27 (50.0)	0.09
CAR-T, n (%)	2 (12.5)	2 (3.7)	0.22
High-risk neutropenia <sup>b</sup> , n (%)	1 (6.3)	3 (5.6)	1.00
Remission, n (%)	7 (43.8)	24 (44.4)	1.00
Vaccine type, n (%)			
mRNA	16 (100.0)	N/A	N/A
Adenovirus vector	0 (0.0)	N/A	N/A
<b>COVID-19 Characteristics</b>			
Last vaccine to infection onset, days, median (IQR)	96.0 (74.5, 126.5)	N/A	N/A

Ever symptomatic, n (%)	15 (93.8)	49 (90.1)	1.00
After delta variant predominant <sup>c</sup> , n (%)	12 (75.0)	3 (5.6)	<b>&lt;0.01</b>
Delta variant <sup>d</sup>	2/3 (66.7)	1/8 (12.5)	0.15
Admission for COVID-19, n (%)	5 (31.3)	13 (24.1)	0.54
Need for supplemental O2, n (%)	5 (31.3)	9 (17.0)	0.29
Need for intubation, n (%)	1 (6.3)	1 (1.9)	0.41
WHO severity score, median (IQR)	2 (2, 4)	2 (2, 2)	0.44
Mortality related to COVID-19, n (%)	1 (6.3)	1 (1.9)	0.41
Treatments received, n (%)			
Monoclonal antibody	11 (68.8)	13 (25.0)	<b>&lt;0.01</b>
Dexamethasone	4 (25.0)	6 (11.1)	0.22
Remdesivir	6 (37.5)	15 (27.8)	0.54
Tocilizumab	1 (6.3)	0 (0.0)	0.23
<b>Serologies</b>			
COVID-19 anti-nucleocapsid IgG <sup>d</sup>			
Positive before infection onset	0/2 (0%)	0/0 (0%)	
Positive within 3 days of infection onset	0/4 (0%)	1/3 (33%)	
Positive >2 weeks after infection onset	1/1 (100%)	3/6 <sup>e</sup> (50%)	
COVID-19 anti-spike IgG <sup>d</sup>			
Positive before infection onset	1/2 (50%)	0/0 (0%)	
Positive within 3 days of infection onset	1/3 (33%)	0/0 (0%)	

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Positive >2 weeks after infection onset

1/1 (100%)

7/8<sup>e</sup> (88%)

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Statistics were performed using Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous and ordinal variables

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T-cell therapy; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; DM, diabetes mellitus; HTN, hypertension; HSCT, hematopoietic stem cell transplant; IQR, interquartile range; O<sub>2</sub>, oxygen; WHO, World Health Organization

<sup>a</sup> Defined as receipt of anti-B-cell therapy within 18 months prior to positive test. Anti-B-cell therapies received were rituximab (n=14) and obinutuzumab (n=1).

<sup>b</sup> Defined as absolute neutrophil count <500 cells/mm<sup>3</sup> for >7 consecutive days in the 3 months prior to positive test

<sup>c</sup> Defined as first positive SARS-CoV-2 test after 6/19/21<sup>15</sup>

<sup>d</sup> Data presented for patients for which this testing was conducted / available

<sup>e</sup> Some patients in this category received COVID-19 vaccinations after infection and before serologies were collected



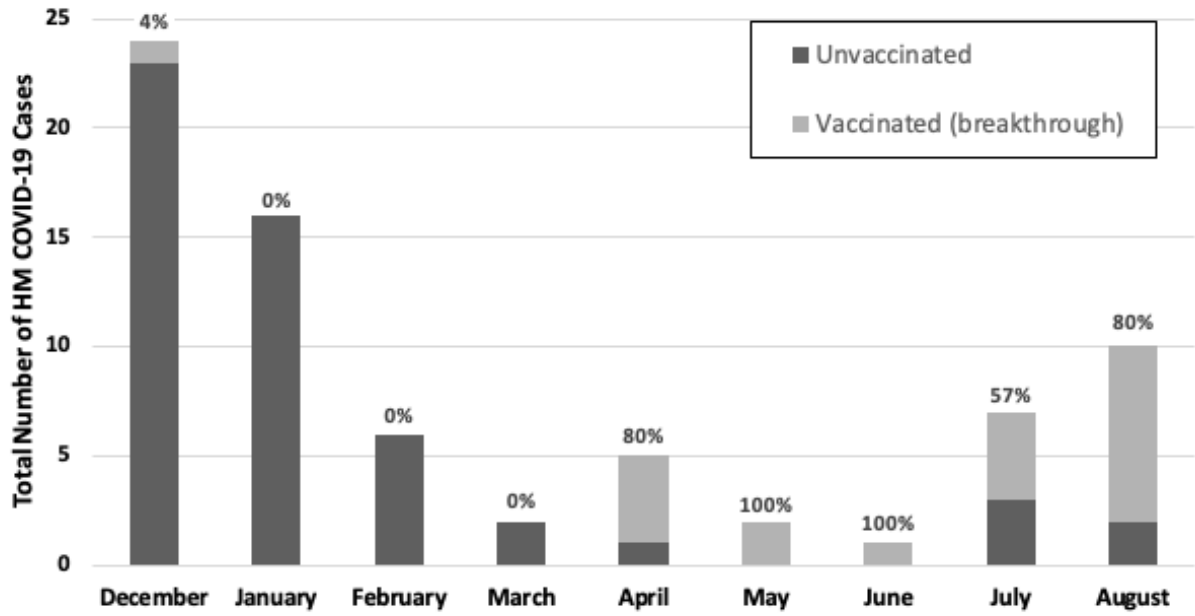


Figure 1. Prevalence of infection after vaccination (“breakthrough”) from December 2020 through August 15th, 2021, as a percentage of all COVID-19 cases in HM patients.