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# Real-World Third COVID-19 Vaccine Dosing and Antibody Response in Patients With Hematologic Malignancies

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**Purpose** This study sought to describe the changes in immune response to a third dose of either Pfizer's or Moderna's COVID-19 mRNA vaccine (3V) among patients with hematologic malignancies, as well as associated characteristics.

**Methods** This retrospective cohort study analyzed pre-3V and post-3V data on 493 patients diagnosed with hematologic malignancies across a large Midwestern health system between August 28, 2021, and November 1, 2021. For antibody testing, S1 spike antigen of the SARS-CoV-2 virus titer was used to determine serostatus.

**Results** Among 493 participants, 274 (55.6%) were seropositive both pre- and post-3V (+/+) while 115 (23.3%) seroconverted to positive from prior negative following the third dose (-/+). The remaining 104 (21.1%) were seronegative both before and after 3V (-/-). No participant was seropositive pre-3V and seronegative post-3V (+/-). Results showed a statistically significant increase in the proportion of seropositivity after receiving a third COVID-19 vaccine (P<0.00001). Response to 3V was significantly associated with the 3V vaccine type (P=0.0006), previous COVID-19 infection (P=0.0453), and malignancy diagnosis (P<0.0001). Likelihood of seroconversion (-/+) after 3V was higher in the group of patients with multiple myeloma or related disorders compared to patients with lymphoid leukemias (odds ratio: 8.22, 95% CI: 2.12–31.79; P=0.0008).

**Conclusions** A third COVID-19 vaccination is effective in producing measurable seroconversion in many patients with hematologic malignancies. Oncologists should actively encourage all their patients, especially those with multiple myeloma, to receive a 3V, given the high likelihood of seroconversion. (*J Patient Cent Res Rev.* 2022;9:149-157.)

**Keywords** hematology; malignancy; COVID-19; SARS-CoV-2; mRNA vaccine; antibody; seroconversion; blood cancer; preventive care

Individuals who are diagnosed with certain cancers are more likely to be at risk for COVID-19-associated complications, severe morbidity, and death.[1-3] Considering one of our best tools to protect individuals against COVID-19 is vaccination, it is of particular concern that certain individuals are less likely to seroconvert after the standard 2-dose COVID-19 mRNA vaccine series manufactured by Pfizer Inc./BioNTech SE or Moderna, Inc.[4-7] With notable exceptions, patients with hematological malignancies (HM) — more commonly known as blood cancers such as leukemia, lymphoma, and multiple myeloma — seem to show a lower response to the standard 2-dose mRNA series when compared to other individuals with other types of cancers.[8] It is thought that the lower response to the standard 2-dose mRNA vaccine series could be due to not only the clinical condition itself but also adjuvant immunosuppressive treatments.[4,8-10]

In a study conducted with 131 patients with cancer who received two mRNA vaccine doses, seroconversion rates were high among the overall cohort (94%); however, among patients with HM, seroconversion rates were significantly lower as compared to those with solid tumors (77% vs 98%, P=0.002).[11] In another recent study, patients with HM, particularly those receiving B cell-depleting immunotherapy, did not gain adequate protection from a standard 2-dose mRNA vaccine or the 1-dose viral vector vaccination series manufactured

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by Johnson & Johnson Services, Inc.[12] Likewise, in two other studies that looked at the spike IgG antibody after a standard 2-dose mRNA vaccine series, patients with HM had some of the lowest responses to the vaccines.[13,14] Moreover, patients with chronic lymphocytic leukemia have shown markedly impaired immune response to COVID-19 mRNA vaccines due to both disease activity and treatment.[15] Spike immunoglobulin G (IgG) antibody titers tend to be highest in cancer patients who are not receiving any cancer therapy or endocrine therapy versus those receiving cytotoxic therapy.[16,17]

There is growing evidence to suggest that a third dose of an approved COVID-19 mRNA vaccine is especially beneficial for HM patients. This dose not only increases the likelihood of added protection against COVID-19-associated morbidity and mortality but also increases the likelihood of seroconversion among individuals who were unresponsive to the standard 2-dose series.[18-20] Furthermore, it is now understood that achieved vaccine-induced immunity against COVID-19 wanes over time, leading to the need of "booster" doses.[21] Given the variability of response to the 2-dose mRNA vaccine series, it is reasonable to approach high-risk patients with a third dose as part of their initial vaccine strategy. When the third dose was first approved in the United States through Emergency Use Authorization, patients with cancer were prioritized.[22] Currently, anyone over the age of 12 is eligible for a booster dose (be it from Pfizer-BioNTech or Moderna) irrespective of immunocompromised status.[23] Despite the universal recommendation by the Centers for Disease Control and Prevention (CDC) for all eligible individuals to get a third dose, many are not doing so, with only 39% having received a third dose as of January 20, 2022.[24]

This study presented herein aimed to document and describe the changes in immune response to a third vaccination dose of mRNA vaccine ("3V") among patients with HM. Data were compiled from an internal systemwide project for which a group of hematologists/oncologists in a large health system serving Illinois and Wisconsin proactively reached out to their HM patient population to encourage a 3V of either U.S. Food and Drug Administration (FDA)-approved mRNA vaccines for COVID-19 and to draw IgG spike protein titers pre- and post-3V to quantify any change in seroconversion. Our primary objective was to quantify the proportion of seropositivity among patients who agreed to have pre- and post-3V titers drawn. A secondary study objective was to describe the characteristics of the patients in each seroconversion category. Of note, a third COVID-19 vaccination is considered part of the primary series in the HM patient population and the term "3V" is used to differentiate it from the "booster" nomenclature suggested for immunocompetent individuals.[25]

## METHODS

This retrospective cohort study analyzed patient data on spike IgG antibody titers pre- and post-3V across Advocate Aurora Health, an integrated U.S. Midwest-based health system consisting of 26 hospitals and more than 500 sites of care. The ADVIA Centaur® SARS-CoV-2 IgG (sCOVG) assay (Siemens Healthineers) was used to provide semi-quantitative (index value) results for the detection of IgG antibodies to the receptor-binding domain of the S1 spike antigen of the SARS-CoV-2 virus. This assay received Emergency Use Authorization from the FDA, and its performance characteristics were validated internally by ACL Laboratories. Assay sensitivity (positive result agreement) was 95.5%, and specificity (negative result agreement) was 99.9%. An index value of >1.00 is considered positive for SARS-CoV-2 IgG antibodies.[26]

### Participants

This study included patients who had been previously diagnosed with HM (Table 1) within the health system between October 31, 2019, and November 1, 2021, and had received the full 2-dose series of a COVID-19 mRNA vaccine, as defined by the CDC,[27] 4 or more weeks prior to 3V. To be eligible for study inclusion, patients had to have their titers drawn equal to or greater than 21 days apart and the pre-titer had to come before or on the same day as 3V, as part of an internal standard of care project.

Patients were excluded from the study if vaccine status was unknown or considered incomplete or if they had received a primary series vaccination that was not an mRNA vaccine manufactured by Moderna and/or Pfizer-BioNTech. Subjects were identified via electronic medical record (EMR) database by the research study team. This study was deemed non-human subjects research by the institutional review board (IRB no. 2021-214) due to the de-identification of data to the study team.

### Variables

Data in this study included demographics, mRNA vaccine type, COVID-19 infection history prior to 3V, days between vaccine doses, HM diagnosis, and up to 4 SARS-CoV-2 IgG antibody results obtained between August 28, 2021 (the date the first titer result appeared in EMR), and November 1, 2021, including days between the 3V of COVID-19 vaccine and each IgG result. Age values less than 90 years were collected as continuous, and the value "Age 90 or older" was recoded as 90. Sex included male and female. Race was collapsed into White, Black, Asian/Pacific Islander, and multiracial (ie, those who identified

**Table 1.** Eligible Hematologic Malignancy Conditions

| Condition | ICD-10 code |
|---|---|
| Hodgkin lymphoma | C81.X* |
| Follicular lymphoma | C82.X |
| Nonfollicular lymphoma | C83.X |
| Mature T/NK-cell lymphomas | C84.X |
| Cutaneous T-cell lymphoma, unspecified | C84.A |
| Other mature T/NK-cell lymphomas | C84.Z |
| Other specified and unspecified types of non-Hodgkin lymphoma | C85.X |
| Other specified types of T/NK-cell lymphoma | C86.X |
| Malignant immunoproliferative diseases and certain other B-cell lymphomas | C88.X |
| Multiple myeloma and malignant plasma cell neoplasms | C90.X |
| Lymphoid leukemia | C91.X |
| Mature B-cell leukemia Burkitt-type | C91.A |
| Other lymphoid leukemia | C91.Z |
| Myeloid leukemia | C92.X |
| Monocytic leukemia | C93.X |
| Other monocytic leukemia | C93.Z |
| Other leukemias of specified cell type | C94.X |
| Leukemia of unspecified cell type | C95.X |
| Other neoplasms of uncertain behavior of lymphoid, hematopoietic, and related tissue | D47.X |
| Eosinophilia | D72.1X |
| Other specified disorders of white blood cells | D72.8X |
| Other and unspecified diseases of blood and blood-forming organs | D75.8X |
| Graft-versus-host disease | D89.81X |

**X indicates subcodes 1–9.*

*ICD-10, International Classification of Diseases, Tenth Revision; NK, natural killer.*

as 2 or more races). Ethnicity included Hispanic/Latino and non-Hispanic/Latino. Unknown values for race and ethnicity were removed from the analysis.

COVID-19 mRNA vaccine type included Pfizer-BioNTech and Moderna. Days between participants' second and third doses of vaccine was collected as continuous. COVID-19 infection history included all EMR-documented positive SARS-CoV-2 polymerase chain reaction (PCR) test results for COVID-19 infection. Diagnosis was recoded and a new category "More than 1 HM condition" was created to make the categories mutually exclusive.

### Statistical Methods

Descriptive statistics are reported as count (column percentage) for categorical variables and as median (range) for numeric values. Demographic and baseline variables are also reported by IgG antibody status before/after receiving 3V.

To assess the primary objective, a McNemar test was used to evaluate the change in proportion of seropositive participants before and after receiving 3V. An exact P-value was calculated. To assess the secondary objective, patients were placed into three groups based on their pre- and post-3V seroconversion categories (-/-, -/+, and +/+). No one went from seropositive to seronegative (+/-), so this fourth grouping was excluded.

Categorical variables were compared using chi-squared test or Fisher's exact test, as appropriate, and continuous variables using a Kruskal Wallis test, with $\alpha$ of $P<0.05$ an indicator of statistical significance. P-values were used to compare each variable among the three groups. Odds ratios (ORs) were calculated for all categorical variables comparing two groups at a time. For OR calculation, -/- was used as the reference outcome because that is the most *undesirable* outcome, thus, ORs compare the other two more "desirable" results, -/+ and +/+, with -/-. Male sex, White race, non-Hispanic/Latino ethnicity, receiving Pfizer-BioNTech as 3V, having previous COVID-19 infection, and having lymphoid leukemia served as the reference groups for those respective variables. Data management and analysis were performed by the study team using R statistical software (version 4.1.1, R Core Team 2021).

## RESULTS

Overall, 514 patients partially met the inclusion criteria. Of those, 10 patients were excluded for not having 2 titer results that were at least 21 days apart and 11 additional patients were excluded for not having the 3V between titers. A total of 493 patients with HM had 2 titer results at least 21 days apart before and after receiving 3V. The median (range) age was 71 (23–90) years, 258 (52.3%) were male, 458 (92.9%) were White, and 479 (98.0%) were non-Hispanic/Latino (Table 2). One patient from the race category and 4 patients from the ethnicity category were excluded for missing/unknown values.

As their 3V, 329 (66.7%) patients received the Pfizer-BioNTech and 164 (33.3%) received the Moderna. A total of 15 (3.0%) patients had a COVID-19 infection prior to receiving 3V. The median (range) days between second and third doses of vaccine was 197 (29–281) days. More than 40% of patients had more than 1 HM condition. The most common individual conditions seen

**Table 2.** Patient Demographics and Characteristics

| Variable | N=493 |
|---|---|
| Age in years, median (range) | 71 (23–90) |
| Sex, n (%) | |
| Male | 258 (52.3%) |
| Female | 235 (47.7%) |
| Race (n=492*), n (%) | |
| White | 458 (93.1%) |
| Black | 26 (5.3%) |
| Asian/Pacific Islander | 7 (1.4%) |
| Multiracial | 1 (0.2%) |
| Ethnicity (n=489*), n (%) | |
| Non-Hispanic/Latino | 479 (98.0%) |
| Hispanic/Latino origin | 10 (2.0%) |
| COVID-19 3V type, n (%) | |
| Pfizer-BioNTech | 329 (66.7%) |
| Moderna | 164 (33.3%) |
| COVID-19 infection pre-3V, n (%) | |
| Yes | 15 (3.0%) |
| No | 478 (97.0%) |
| Days between dose 2 and dose 3, median (range) | 197 (29–281) |
| Clinically designated ICD-10 diagnosis, n (%) | |
| Lymphoid leukemia (including ALL and CLL) | 88 (17.8%) |
| Multiple myeloma and malignant plasma cell neoplasms (including dyscrasias) | 66 (13.4%) |
| Nonfollicular lymphoma | 44 (8.9%) |
| Follicular lymphoma | 25 (5.1%) |
| Myeloid leukemia (including AML and CML) | 23 (4.7%) |
| Other specific and unspecified types of non-Hodgkin lymphoma | 16 (3.2%) |
| Hodgkin lymphoma | 9 (1.8%) |
| Other and unspecified diseases of blood and blood-forming organs | 6 (1.2%) |
| Other neoplasms of uncertain behavior of lymphoid, hematopoietic, and related tissue | 6 (1.2%) |
| Other specified disorders of white blood cells | 5 (1%) |
| Malignant immunoproliferative diseases and certain other B-cell lymphomas | 4 (0.8%) |
| Mature T/NK-cell lymphomas | 3 (0.6%) |
| >1 hematologic malignancy condition | 198 (40.2%) |

**Unknown values for race and ethnicity were removed, resulting in the reduced number of participants shown for those variables.*

*ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL. chronic lymphocytic leukemia; CML, chronic myeloid leukemia; ICD-10, International Classification of Diseases, Tenth Revision; NK, natural killer.*

in the cohort were lymphoid leukemia (17.8%), multiple myeloma and malignant plasma cell neoplasms (13.4%), and nonfollicular lymphoma (8.9%).

### Primary Outcome: Proportion of Seropositivity

Among 493 participants, 274 (55.6%) were seropositive pre-3V and 389 (78.9%) were seropositive post-3V (Table 3). Specifically, 274 (55.6%) were seropositive both pre- and post-3V (+/+) while 115 (23.3%) seroconverted to positive from prior negative following 3V (-/+). The remaining 104 (21.1%) were seronegative both before and after 3V (-/-). No participant was seropositive pre-3V and seronegative post-3V (+/-). Results from the exact McNemar test showed a statistically significant increase in the proportion of seropositivity after receiving a third COVID-19 vaccine (P<0.0001).

### Secondary Outcome: Characteristics Associated With 3V Response

Response to 3V was significantly associated with 3V vaccine type (P=0.0006), previous COVID-19 infection (P=0.0453), and HM cancer type (P<0.0001) (Table 4). Table 5 shows the odds for seroconversion (-/+) in patients with multiple myeloma and malignant plasma cell neoplasms were higher as compared to patients with lymphoid leukemia (OR: 8.22, 95% CI: 2.12–31.79; P=0.0008). The odds for being seropositive (+/+) was greater in those who received Moderna than those who received Pfizer-BioNTech (OR: 2.40, 95% CI: 1.42–4.02; P<0.0008).

Within the HM diagnoses, the odds for being seropositive (+/+) were higher in patients with multiple myeloma and other plasma cell dyscrasias (OR: 11.40, 95% CI: 3.22–40.31; P<0.0001), in patients with myeloid leukemia (OR: 16.36, 95% CI: 2.08–128.46; P=0.0007), and in patients with more than 1 HM condition (OR: 1.84, 95% CI: 1.01–3.35; P=0.0447), all as compared to patients with lymphoid leukemia (Table 5).

**Table 3.** Changes in IgG Antibody Response

| Pre-3V titer result | Post-3V titer result[a] | | |
|---|---|---|---|
| | **Positive** | **Negative** | **Total** |
| Positive | 274 (55.6%) | 0 (0%) | 274 (55.6%) |
| Negative | 115 (23.3%) | 104 (21.1%) | 219 (44.4%) |
| Total | 389 (78.9%) | 104 (21.1%) | 493 |
| **Vaccination status** | **Proportion of seropositivity** | | ***P*[b]** |
| Pre-3V | 55.6% | | <0.0001[c] |
| Post-3V | 78.9% | | |

*[a]Percentages out of total number of participants (n=493).*

*[b]As determined by McNemar test.*

*[c]Binomial distribution used; α of 0.05 defined significance.*

*3V, third dose of mRNA vaccine; IgG, immunoglobulin G.*

## DISCUSSION

The COVID-19 pandemic has evolved rapidly, and more infectious variants are becoming rapidly prevalent worldwide. An effective vaccine strategy is still believed to offer the best protection against severe illness, especially for vulnerable populations.[28] However, response to the standard 2-dose mRNA vaccine strategy is not universally effective.[29,30] We present a large series of patients with HM that shows only about 50% of these patients have adequate IgG titer presence following standard 2-dose mRNA vaccination. Furthermore, our data demonstrate that over half of formerly non-seroconverted patients do seroconvert with a 3V of either mRNA vaccine. Given the increased risk of COVID-19-associated morbidity and mortality among HM patients with HM, along with the added increased likelihood of not seroconverting after the standard 2-dose mRNA series, it is imperative to offer a 3V to this patient population, albeit the timing of treatment, vaccination, and relationship to disease status (eg stable vs progressive) is complicated.

The clinical implications of our findings recommend that oncologists should actively encourage their patients to receive 3V, citing this and other similar data, as evidence of high likelihood of seroconversion and thus more protection against severe morbidity and mortality caused by COVID-19. This is especially true for their those diagnosed with multiple myeloma and plasma cell dyscrasias, patients who appear to have a high seroconversion rate after 3V and who should consider themselves persistently highly vulnerable to negative outcomes following COVID-19 exposure.

Limitations of our study dataset included the lack of T-cell function testing. Also, testing results lack correlation to clinical outcomes due to the short timeline between 3V and publication. Our study design did not include accessing immunosuppressant treatment data. We continue to follow our study population for COVID-19 infection and associated morbidity and mortality and plan to publish such data at a future time. Future research should explore ways to improve seroconversion, such as with additional or higher doses of COVID-19 vaccine. Future research also could investigate whether the administration of different vaccine types for the first two and third doses affects rate of seroconversion, as the number of patients from our study falling into that camp (n=27) was too small to adequately analyze.

**Table 4.** Patient Characteristics Associated With Paired IgG Results Before and After 3V

| Characteristic | -/- n=104 (21.1%) | -/+ n=115 (23.3%) | +/+ n=274 (55.6%) | *P* |
|---|---|---|---|---|
| Age (median, range) | 72 (36–90) | 72 (23–90) | 70 (27–90) | 0.3180 |
| Sex | | | | 0.1587 |
| Male | 63 (60.6%) | 59 (51.3%) | 136 (49.6%) | |
| Female | 41 (39.4%) | 56 (48.7%) | 138 (50.4%) | |
| Race[a] | *n=104* | *n=115* | *n=273* | 0.1833 |
| White | 101 (97.1%) | 103 (89.6%) | 254 (93.0%) | |
| Black | 2 (1.9%) | 8 (7.0%) | 16 (5.9%) | |
| Asian/Pacific Islander | 1 (1.0%) | 3 (2.6%) | 3 (1.1%) | |
| Multiracial | 0 (0.0%) | 1 (0.9%) | 0 (0.0%) | |
| Ethnicity[a] | *n=104* | *n=114* | *n=271* | >0.9999 |
| Non-Hispanic/Latino | 102 (98.1%) | 112 (98.2%) | 265 (97.8%) | |
| Hispanic/Latino origin | 2 (1.9%) | 2 (1.8%) | 6 (2.2%) | |
| COVID-19 3V type | | | | 0.0006[b] |
| Pfizer-BioNTech | 81 (77.9%) | 85 (73.9%) | 163 (59.5%) | |
| Moderna | 23 (22.1%) | 30 (26.1%) | 111 (40.5%) | |
| COVID-19 infection pre-3V | | | | 0.0453[c] |
| Yes | 3 (2.9%) | 0 (0.0%) | 12 (4.4%) | |
| No | 101 (97.1%) | 115 (100.0%) | 262 (95.6%) | |
| Days between dose 2 and dose 3 (median, range) | 190 (80–260) | 197 (106–276) | 199.5 (29–281) | 0.0634 |
| Diagnosis | | | | <0.0001[b,d] |
| Lymphoid leukemia | 29 (27.9%) | 20 (17.4%) | 39 (14.2%) | |
| Multiple myeloma and malignant plasma cell neoplasms | 3 (2.9%) | 17 (14.8%) | 46 (16.8%) | |
| Nonfollicular lymphoma | 14 (13.5%) | 9 (7.8%) | 21 (7.7%) | |
| Follicular lymphoma | 8 (7.7%) | 7 (6.1%) | 10 (3.6%) | |
| Myeloid leukemia | 1 (1%) | 0 (0%) | 22 (8%) | |
| Other specific and unspecified types of non-Hodgkin lymphoma | 5 (4.8%) | 2 (1.7%) | 9 (3.3%) | |
| Hodgkin lymphoma | 0 (0%) | 2 (1.7%) | 7 (2.6%) | |
| Other and unspecified diseases of blood and blood-forming organs | 0 (0%) | 2 (1.7%) | 4 (1.5%) | |
| Other neoplasms of uncertain behavior of lymphoid, hematopoietic, and related tissue | 0 (0%) | 2 (1.7%) | 4 (1.5%) | |
| Other specified disorders of white blood cells | 0 (0%) | 1 (0.9%) | 4 (1.5%) | |
| Malignant immunoproliferative diseases and certain other B-cell lymphomas | 1 (1%) | 0 (0%) | 3 (1.1%) | |
| Mature T/NK-cell lymphomas | 1 (1%) | 1 (0.9%) | 1 (0.4%) | |
| >1 hematologic malignancy condition | 42 (40.4%) | 52 (45.2%) | 104 (38%) | |

*[a]Unknown values for race and ethnicity were removed, resulting in reduced number of participants shown for those variables.*

*[b]Statistically significant at P<0.01 for chi-squared test (or Fisher's exact test) if categorical and Kruskal-Wallis test if continuous.*

*[c]Statistically significant at P<0.05 for chi-squared test (or Fisher's exact test) if categorical and Kruskal-Wallis test if continuous.*

*[d]Generated using Monte Carlo simulation with 10,000 iterations.*

*3V, third dose of mRNA vaccine; IgG, immunoglobulin G; NK, natural killer.*

**Table 5.** Odds Ratios of Paired IgG Results Associated With Patient Characteristics

| | -/+ vs -/- (ref) | | +/+ vs -/- (ref) | |
|---|---|---|---|---|
| **Characteristic** | **Odds ratio (95% CI)** | ***P*[a]** | **Odds ratio (95% CI)** | ***P*[a]** |
| Sex | | | | |
| Male | ref | | ref | |
| Female | 1.46 (0.85, 2.50) | 0.1677 | 1.56 (0.99, 2.47) | 0.0571 |
| Race | | | | |
| White | ref | | ref | |
| Black | 3.92 (0.81, 18.92) | 0.1036 | 3.18 (0.72, 14.09) | 0.1737 |
| Asian/Pacific Islander | 2.94 (0.30, 28.75) | 0.6216 | 1.19 (0.12, 11.60) | >0.9999 |
| Multiracial | – | >0.9999 | – | >0.9999 |
| Ethnicity | | | | |
| Non-Hispanic/Latino | ref | | ref | |
| Hispanic/Latino origin | 0.91 (0.13, 6.58) | >0.9999 | 1.15 (0.23, 5.81) | >0.9999 |
| COVID-19 3V typed | | | | |
| Pfizer-BioNTech | ref | | ref | |
| Moderna | 1.24 (0.67, 2.32) | 0.4932 | 2.40 (1.42, 4.04)[b] | 0.0008[b] |
| COVID-19 infection pre-3V | | | | |
| Yes | ref | | ref | |
| No | – | 0.1055 | 0.65 (0.18, 2.35) | 0.7684 |
| Diagnosis | | | | |
| Lymphoid leukemia | ref | | ref | |
| Multiple myeloma and malignant plasma cell neoplasms | 8.22 (2.12, 31.79)[b] | 0.0008[b] | 11.40 (3.22, 40.31)[b] | <0.0001[b] |
| Nonfollicular lymphoma | 0.93 (0.34, 2.57) | 0.8918 | 1.12 (0.49, 2.56) | 0.7964 |
| Follicular lymphoma | 1.27 (0.40, 4.06) | 0.6881 | 0.93 (0.33, 2.65) | 0.8911 |
| Myeloid leukemia | 0 (0, NA) | >0.9999 | 16.36 (2.08, 128.46)[b] | 0.0007[b] |
| Other specific and unspecified types of non-Hodgkin lymphoma | 0.58 (0.10, 3.29) | 0.6920 | 1.34 (0.41, 4.42) | 0.6316 |
| Hodgkin lymphoma | – | 0.1812 | – | 0.0388[c] |
| Other and unspecified diseases of blood and blood-forming organs | – | 0.1812 | – | 0.1430 |
| Other neoplasms of uncertain behavior of lymphoid, hematopoietic, and related tissue | – | 0.1812 | – | 0.1430 |
| Other specified disorders of white blood cells | – | 0.4200 | – | 0.1430 |
| Malignant immunoproliferative diseases and certain other B-cell lymphomas | 0 (0, NA) | >0.9999 | 2.23 (0.22, 22.56) | 0.6359 |
| Mature T/NK-cell lymphomas | 1.45 (0.09, 24.56) | >0.9999 | 0.74 (0.04, 12.39) | >0.9999 |
| >1 hematologic malignancy condition | 1.80 (0.89, 3.61) | 0.0997 | 1.84 (1.01, 3.35)[c] | 0.0447[c] |

[a]*Based on direct differences between the variable level relative to the reference level of the same variable.*

[b]*Statistically significant at P<0.01 for chi-squared test (or Fisher's exact test).*

[b]*Statistically significant at P<0.05 for chi-squared test (or Fisher's exact test).*

[d]*27 patients received different vaccine types for their second and third doses. Given the small number, this analysis focused on 3V dose type only.*

*3V, third dose of mRNA vaccine; IgG, immunoglobulin G; NA, not available; NK, natural killer; ref, reference value.*

## CONCLUSIONS

A third COVID-19 vaccination is effective in producing measurable seroconversion in many patients with hematologic malignancy. Vaccine response was significantly associated with 3V vaccine type, previous COVID-19 infection, and specific HM condition. Given these results, we believe that cancer care providers should strongly encourage additional vaccine doses for their patients, especially those with plasma cell disorders. For patients with lymphoid malignancies, a single 3V vaccine approach may not be as beneficial and other protective approaches should be pursued (eg, antibody therapy, postexposure antiviral therapy).

### Patient-Friendly Recap

- mRNA vaccines provide robust protection against severe illness from COVID-19. However, in patients highly vulnerable to infection like those receiving treatment for blood cancer, more doses may be necessary to reach desired immunity levels.
- Authors found that more than half of patients with hematologic malignancy whose IgG antibodies were inadequate after 2 vaccine doses achieved protection after a third dose.
- Given increased risk of COVID-19-associated mortality for patients with multiple myeloma or plasma cell disorders, oncologists should actively encourage a 3-dose vaccine series, accounting for treatment/disease status.
- For patients with lymphoid malignancies, a 3-dose series may not be as beneficial and other protective approaches should be pursued.

### Author Contributions

Study design: Thompson, Hallmeyer, Fitzpatrick, Mullane, Medlin, Weese. Data acquisition or analysis: Fitzpatrick, Liao. Manuscript drafting: Thompson, Hallmeyer, Fitzpatrick. Critical revision: Mullane, Medlin, Copeland, Weese.

### Conflicts of Interest

None.

### References


1. Griffiths E, Segal B. Immune responses to COVID-19 vaccines in patients with cancer: promising results and a note of caution. *Cancer Cell.* 2021;39:1045-7. CrossRef
2. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov.* 2021;10:783-91. CrossRef
3. Centers for Disease Control and Prevention. Underlying medical conditions associated with higher risk for severe COVID-19: information for healthcare providers. Page updated June 15, 2022; accessed January 15, 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
4. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood.* 2020;136:2881-92. CrossRef
5. Seebacher NA. The antibody response of haematological malignancies to COVID-19 infection and vaccination. *Br J Cancer.* 2022;126:691-2. CrossRef
6. Thakkar A, Gonzalez-Lugo JD, Goradia N, et al. Seroconversion rates following COVID-19 vaccination among patients with cancer. *Cancer Cell*. 2021;39:1081-90.e2. CrossRef
7. Addeo A, Shah PK, Bordry N, et al. Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer. *Cancer Cell*. 2021;39:1091-8.e2. CrossRef
8. Fendler A, Shepherd ST, Au L, et al. Immune responses following third COVID-19 vaccination are reduced in patients with hematological malignancies compared to patients with solid cancer. *Cancer Cell*. 2022;40:114-6. CrossRef
9. Massarweh A, Eliakim-Raz N, Stemmer A, et al. Evaluation of seropositivity following BNT162b2 messenger RNA vaccination for SARS-CoV-2 in patients undergoing treatment for cancer. *JAMA Oncol*. 2021;7:1133-40. CrossRef
10. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant. *JAMA*. 2021;325:2204-6. CrossRef
11. Ollila TA, Lu S, Masel R, et al. Antibody response to COVID-19 vaccination in adults with hematologic malignant disease. *JAMA Oncol.* 2021;7:1714-6. CrossRef
12. Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nicols GL. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. *Cancer Cell.* 2021;39:1031-3. CrossRef
13. Bird S, Panopoulou A, Shea RL, et al. Response to first vaccination against SARS-CoV-2 in patients with multiple myeloma. *Lancet Haematol.* 2021;8:e389-92. CrossRef
14. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood.* 2021;137:3165-73. CrossRef
15. Agha M, Blake M, Chilleo C, Wells A, Haidar G. Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients. (preprint). *medRxiv*. Epub 2021 Apr 7. CrossRef
16. Chan L, Fuca N, Zeldis E, Campbell KN, Shaikh A. Antibody response to mRNA-1273 SARS-CoV-2 vaccine in hemodialysis patients with and without prior COVID-19. *Clin J Am Soc Nephrol.* 2021;16:1258-60. CrossRef
17. Rottenberg Y, Grinshpun A, Ben-Dov IZ, Oiknine Djian E, Wolf DG, Kadouri L. Assessment of response to a third dose of the SARS-CoV-2 BNT162b2 mRNA vaccine in patients with solid tumors undergoing active treatment. *JAMA Oncol.* 2022;8:300-1. CrossRef
18. Cattaneo C, Cancelli V, Imberti L, et al. Production and persistence of specific antibodies in COVID-19 patients with hematologic malignancies: role of rituximab. *Blood Cancer J.* 2021;11(9):151. CrossRef

19. Re D, Seitz-Polski B, Brglez V, et al. Humoral and cellular responses after a third dose of SARS-CoV-2 BNT162b2 vaccine in patients with lymphoid malignancies. *Nat Commun*. 2022;13(1):864. CrossRef
20. Gong IY, Vijenthira A, Betschel SD, Hicks LK, Cheung MC. COVID-19 vaccine response in patients with hematologic malignancy: a systematic review and meta-analysis. *Am J Hematol*. 2022;97:E132-5. CrossRef
21. Terpos E, Gavriatopulou M, Ntanasis-Stathopoulos I, et al. Booster BNT162b2 optimizes SARS-CoV-2 humoral response in myeloma patients; the negative effect of anti-BCMA therapy. *Blood*. 2022;139:1409-12. CrossRef
22. U.S. Food and Drug Administration. FDA authorizes booster dose of Pfizer-BioNTech COVID-19 vaccine for certain populations. Released September 22, 2021; accessed December 15, 2021. https://www.fda.gov/news-events/press-announcements/fda-authorizes-booster-dose-pfizer-biontech-covid-19-vaccine-certain-populations
23. Centers for Disease Control and Prevention. CDC expands booster shot eligibility and strengthens recommendations for 12-17 year olds. Released January 5, 2022; accessed January 10, 2022. https://www.cdc.gov/media/releases/2022/s0105-Booster-Shot.html
24. Centers for Disease Control and Prevention. COVID-19 vaccinations in the United States. Data accessed January 15, 2021. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-totalCdc%20booster%20eligibility
25. Centers for Disease Control and Prevention. COVID-19 vaccines for moderately or severely immunocompromised people. Page updated June 30, 2022; accessed January 15, 2022. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html
26. Siemens Healthcare Diagnostics Inc. Fact sheet for healthcare providers: ADVIA Centaur SARS-CoV-2 IgG (sCOVG). Issued August 10, 2021; accessed January 15, 2022. https://www.fda.gov/media/150236/download
27. Centers for Disease Control and Prevention. Use of COVID-19 vaccines in the United States: interim clinical considerations. Page last reviewed June 24, 2022; accessed January 15, 2022. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#primary-series
28. Lee ARYB, Wong SY, Chai LYA, et al. Efficacy of COVID-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *BMJ*. 2022;376:e068632. CrossRef
29. Gounant V, Ferré VM, Soussi G, et al. Efficacy of severe acute respiratory syndrome coronavirus-2 vaccine in patients with thoracic cancer: a prospective study supporting a third dose in patients with minimal serologic response after two vaccine doses. *J Thorac Oncol*. 2022;17:239-51. CrossRef
30. Espi M, Charmetant X, Barba T, et al. A prospective observational study for justification, safety, and efficacy of a third dose of mRNA vaccine in patients receiving maintenance hemodialysis. *Kidney Int*. 2022;101:390-402. CrossRef