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Evaluation Of Antibody Response To Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination In Patients With Lymphoid And Solid Organ Malignancies

Mukul Singal
Rochester Regional Health System, mukul.singal@rochesterregional.org

Sanjana Kalvehalli Kashinath
Rochester Regional Health System, Sanjana.Kashinath@rochesterregional.org

S. Shahzad Mustafa
Rochester Regional Health System, shahzad.mustafa@rochesterregional.org

Edward Walsh
Rochester Regional Health System, Edward.Walsh@rochesterregional.org

Karthik Vadamalai
Mercy Hospital Springfield, Springfield, MO, karrochester13@gmail.com

Saad Jamshed
Rochester Regional Health System, Saad.Jamshed@rochesterregional.org

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current COVID-19 pandemic. There is emerging evidence regarding suboptimal response to vaccination against COVID-19 in patients with hematologic and solid organ malignancies.

We conducted a single-center prospective study assessing seroconversion in response to vaccination against COVID-19 in 53 patients with chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), and solid organ malignancies.

A quantitative immunoassay of IgG antibodies to SARS-CoV-2 Spike (S) protein was measured prior to vaccination and at 2 weeks after completion of two-dose vaccination series. A fourfold increase in antibody titers was considered positive seroconversion. Through a predesigned survey, patients also self-reported side effects from each dose of vaccination.

Seroconversion on vaccination was seen in 6/12 (50%) patients with CLL, 7/11 (63.6%) patients with NHL, 9/10 (90%) patients with MM, and 17/20 (85%) patients with solid organ malignancy. Only 6 of the 14 (42.8%) patients currently on or with previous history of rituximab use seroconverted. Injection site soreness was the most reported side effect. The only severe side effect occurred in a patient with solid organ malignancy who developed Parsonage-Turner syndrome.

Patients with CLL and NHL appear less likely to respond to vaccination against COVID-19 in contrast to patients with MM or solid organ malignancies. Previous treatment with

rituximab is a possible risk factor for suboptimal response to vaccination.

These data highlight the importance of continuing risk mitigation strategies against COVID-19 in individuals with hematologic malignancy, particularly those with CLL or on treatment with rituximab.

Keywords

covid 19, vaccination, immunization, seroconversion, immunocompromised

Conflict of Interest Statement

Mukul Singal, Sanjana Kalvehalli Kashinath, and Karthik Vadamalai declare no conflicts of interest. S. Shahzad Mustafa Speakers Bureau- Genetech Speakers Bureau- Glaxosmithkline Speakers Bureau- CSL Behring Speakers Bureau- Regeneron Speakers Bureau- AstraZeneca Edward Walsh Research Funding- Janssen Research Funding- Merck Research Funding- Pfizer Saad Jamshed Speakers Bureau- Takeda Honoraria- Bristol Meyers Squibb

CLINICAL TRIAL

Evaluation of Antibody Response to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination in Patients with Lymphoid and Solid Organ Malignancies

Mukul Singal [a], Sanjana K. Kashinath [a], S. Shahzad Mustafa [a,c], Edward Walsh [a], Karthik Vadamalai [b], Saad Jamshed [a,*]

[a] Rochester Regional Health System, USA
[b] Mercy Hospital Springfield, Springfield, MO, USA
[c] University of Rochester School of Medicine and Dentistry, USA

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current COVID-19 pandemic. There is emerging evidence regarding suboptimal response to vaccination against COVID-19 in patients with hematologic and solid organ malignancies.

We conducted a single-center prospective study assessing seroconversion in response to vaccination against COVID-19 in 53 patients with chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), and solid organ malignancies.

A quantitative immunoassay of IgG antibodies to SARS-CoV-2 Spike (S) protein was measured prior to vaccination and at 2 weeks after completion of two-dose vaccination series. A fourfold increase in antibody titers was considered positive seroconversion. Through a predesigned survey, patients also self-reported side effects from each dose of vaccination.

Seroconversion on vaccination was seen in 6/12 (50%) patients with CLL, 7/11 (63.6%) patients with NHL, 9/10 (90%) patients with MM, and 17/20 (85%) patients with solid organ malignancy. Only 6 of the 14 (42.8%) patients currently on or with previous history of rituximab use seroconverted. Injection site soreness was the most reported side effect. The only severe side effect occurred in a patient with solid organ malignancy who developed Parsonage-Turner syndrome.

Patients with CLL and NHL appear less likely to respond to vaccination against COVID-19 in contrast to patients with MM or solid organ malignancies. Previous treatment with rituximab is a possible risk factor for suboptimal response to vaccination.

These data highlight the importance of continuing risk mitigation strategies against COVID-19 in individuals with hematologic malignancy, particularly those with CLL or on treatment with rituximab.

Keywords: covid 19, Vaccination, Immunization, Seroconversion, Immunocompromised

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that has led to a global pandemic. The Food and Drug Administration has approved or authorized mRNA vaccine BNT162b2 (Pfizer), mRNA-1273 (Moderna), and viral vector vaccine JNJ-78436735 (Janssen) in the USA. These vaccines have shown significant efficacy against COVID-19, particularly in preventing severe infection and death.[1–3]

Patients with hematological malignancies are at higher risk of not only contracting COVID-19 infection but also COVID-19-related complications, with mortality reported to be as high as 30%.[4,5] The increased morbidity and mortality are due to both

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* Corresponding author.
E-mail address: Saad.Jamshed@rochesterregional.org (S. Jamshed).

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inherent immune dysfunction in these conditions, as well as additional immune suppressive effects of therapeutic regimens, such as anti-B-cell therapies.[6–9] Initial studies leading to the availability of COVID-19 vaccines did not include immunocompromised patients, such as those with B-cell malignancies or those treated with B-cell-depleting therapies. Extensive literature has shown that these patients respond suboptimally to various vaccines, leaving them at increased risk of infectious complications.[10,11] Therefore, it is essential to evaluate if patients with B-cell malignancies will mount an appropriate antibody response with vaccination against COVID-19.

To address this knowledge gap, our study prospectively measured the antibody response to the COVID-19 vaccines in patients with chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), and those with solid organ malignancy.

2. Methods

2.1. Data source and cohort collection

We conducted this single-center prospective cohort study in a tertiary care community hospital and patients were recruited from three hematology/oncology clinics and one allergy/immunology clinic between March 8, 2021, and June 1, 2021. Adult patients with a diagnosis of CLL, MM, and NHL and solid tumors who were on treatment were identified based on a review of the local patient registry and physician referral. Of the patients approached, we included the patients who were willing to be vaccinated against COVID-19, consented to blood draws, and agreed to complete a post-vaccination questionnaire on vaccine side effects. Patients with a prognosis estimated to be less than 6 months were not included in the study. The same assay was previously validated in hospital staff members without previous COVID-19 infection (based on the absence of symptoms, and absence of antibodies to SARS-CoV-2 nucleocapsid protein on the assay). Post-vaccination titers (two weeks after the second dose of an mRNA vaccine or four weeks after a single dose of the viral vector vaccine) were collected for these healthy volunteers. 21 of these healthy volunteers (henceforth referred to as controls), who did not have a previous history of malignancy or immunosuppression, are presented for comparison to our study population (Table 1). A survey of adverse effects was collected in person at the time of the final blood draw for serology from the study subjects. The study was approved by the institutional review board.

Table 1. Data for subjects considered controls.

	Age	Gender	Vaccine	Titer	Comorbid Conditions							
					CHF	CAD	COPD	CLD	CKD	Autoimmune ds	DM	Cancer
1	75	F	Pfizer	15.70	–	–	–	+	–	–	–	–
2	70	F	Moderna	15.70	–	–	–	–	+	Hashimoto's thyroiditis	–	–
3	69	F	Moderna	16.20	–	–	–	–	–	–	–	–
4	90	F	Moderna	15.70	–	–	–	–	–	–	–	–
5	70	F	Pfizer	15.20	–	–	–	–	–	–	–	–
6	66	F	Moderna	16.20	–	–	–	–	–	–	–	–
7	78	F	Pfizer	13.70	–	–	–	–	–	–	–	–
8	69	F	Pfizer	15.70	–	–	–	–	–	–	–	–
9	68	M	Pfizer	14.70	–	–	–	–	–	–	–	–
10	72	M	Pfizer	13.70	–	–	–	–	–	–	–	–
11	48	F	Pfizer	16.47	–	–	–	–	–	–	–	–
12	62	F	Pfizer	15.97	–	–	–	–	–	–	–	–
13	58	M	Pfizer	14.47	–	–	–	–	–	–	–	–
14	63	F	Pfizer	16.47	–	–	–	–	–	–	–	–
15	65	F	Pfizer	15.97	–	–	–	–	–	–	–	–
16	38	F	Moderna	16.47	–	–	–	–	–	–	–	–
17	66	F	Pfizer	13.47	–	–	–	–	–	–	–	–
18	67	F	Pfizer	15.97	–	–	–	–	–	–	–	–
19	67	M	Pfizer	12.97	–	–	–	–	–	–	–	–
20	*67*	*F*	*Pfizer*	*15.97*	-	–	–	–	–	–	–	–
21	*68*	*F*	*Pfizer*	*12.97*	-	–	–	–	–	–	–	–

Titers and baseline demographics for subjects considered as controls for comparison. None of the subjects had underlying malignancy or a known immunosuppressive state. None of the controls had prior COVID-19 infection (based on the absence of symptoms, absence of positive tests, and absence of antibodies to SARS CoV-2 nucleocapsid protein). CHF: history of congestive heart failure; CAD: history of coronary artery disease; COPD: history of chronic obstructive pulmonary disease; CLD: history of chronic liver disease; CKD: history of chronic kidney disease; DM: history of diabetes mellitus, autoimmune ds: history of autoimmune disease.

2.2. Statistical analysis

Descriptive statistics were used for this cohort study. Microsoft Excel software (Office 365, Microsoft Corporation, Redmond, WA 98052) was used for statistical analysis and graphs. Baseline characteristics for the study patients are reported in medians and interquartile ranges. Results are described in percentages and as graphs. The healthy subjects used as "controls" were not directly compared to the subjects in the study and differences between these two groups were not evaluated statistically.

2.3. Variables and endpoints

Antibody titers were measured before the first dose of vaccination (baseline) for all patients, two weeks after the second dose of an mRNA vaccine, or four weeks after a single dose of the viral vector vaccine (post-vaccination titer). We measured the serum titers of IgG to SARS-CoV-2 Spike (S) protein and nucleocapsid (N) protein by enzyme immunoassay (EIA) using standard methods in our laboratory. Briefly, the viral antigens (S, N, control) were coated on a 96-well EIA plate overnight, followed by the addition of serial two-fold dilutions of the patient's serum and incubation at room temperature overnight. The plates were then rewashed, and alkaline phosphatase-conjugated goat-anti human IgG is added for 3 hours, followed by the addition of substrate. The color development was quantified spectrophotometrically, and the IgG titer to each antigen was determined after subtraction of background reactivity (control plate) was reported. Inter and Intra assay variability was controlled using a high, medium, and low titer and a standard COVID-19 convalescent serum in each assay run. A fourfold increase in titers (2 $\log_2$) was considered an adequate vaccine response.

3. Results

3.1. Baseline patient demographics

The study enrolled 56 patients between March 8, 2021, and June 1, 2021, and 53 were included in the final analysis because two patients decided not to pursue vaccination and one patient transitioned to hospice care shortly after enrollment. Of the 53 patients, 12 had CLL, 10 had multiple myeloma, 11 had NHL and 20 had solid malignancies (Table 2). The median age was 61 years (IQR: 58−69), 84.9% of patients were Caucasian and 56.6% were female. A majority of the patients were vaccinated with the BNT162b2 vaccine (75.4%), followed by mRNA-1273 (16.9%) and JNJ-78436735 vaccines (7.5%).

3.2. Response to vaccination

3.2.1. CLL

Six of the twelve patients (50%) demonstrated seroconversion with vaccination (Figs. 1 and 2) (Table 3). Three of the twelve patients were actively receiving chemotherapy, (chlorambucil, venetoclax, and venetoclax with rituximab respectively) and none of them demonstrated seroconversion. Of the four patients with CLL who were currently on, or had a history of rituximab use, only one patient demonstrated seroconversion. Of the four patients with CLL receiving immunoglobulin replacement, two (50%) demonstrated seroconversion.

3.3. Non-Hodgkin's lymphoma

Seven out of these eleven patients (63.6%) demonstrated seroconversion with vaccination (Figs. 1 and 2). Only one patient was actively receiving chemotherapy (brentuximab, cyclophosphamide, Adriamycin, and prednisone) and seroconverted on vaccination. Of the nine patients with a history of rituximab use, five (55.5%) were seroconverted. One of the two NHL patients (50%) who were on immunoglobulin replacement demonstrated seroconversion. The one NHL patient who had undergone an autologous hematopoietic stem cell transplant did not seroconvert on vaccination.

3.4. Multiple myeloma

Nine of the ten patients (90%) with multiple myeloma demonstrated seroconversion with vaccination, eight of the nine patients (88.8%) receiving treatment, and all seven of the patients (100%) who had undergone autologous hematopoietic stem cell transplant (Figs. 1 and 2) seroconverted on vaccination. The single patient in the MM group who did not respond to vaccination was on induction therapy with lenalidomide, bortezomib, dexamethasone, and daratumumab.

3.5. Solid-organ malignancies

We included patients with solid organ malignancies who were on treatment (hormone therapy, targeted therapy, immunotherapy, or chemotherapy). Seventeen of the twenty patients (85%) with solid organ malignancy demonstrated seroconversion with vaccination (Figs. 1 and 2). Fifteen of the eighteen patients (90%) with solid organ malignancy who were actively receiving therapy seroconverted on vaccination. All seven patients receiving endocrine therapy (100%), three of the six

Table 2. Patient demographics.

Baseline Characteristics	N = 53 (100%)
	n (% of Total)
Age	61 (58−69)
Female	30 (56.6%)
BMI	28.4 (24.2−34.3)
Ethnicity	
African American	7 (13.2%)
Caucasian	45 (84.9%)
Other	1 (1.8%)
Time since diagnosis of cancer (in months)	42 (12−84)
Currently on cancer therapy	31 (58.5%)
History of COVID 19 infection prior to vaccination	3 (5.6%)
Type of malignancy	
CLL	12 (22.6%)
Myeloma	10 (18.8%)
Lymphoma	11 (20.7%)
Solid tumor	20 (37.7%)
Treatment	
Monoclonal antibodies	
History of rituximab use	13 (24.5%)
Current use of monoclonal antibodies	2 (3.8%)
- Brentuximab	1 (1.8%)
- Rituximab	1 (1.8%)
Immunoglobulin replacement	
Past and/or current use	10 (18.9%)
History of immunoglobulin replacement	7 (13.2%)
Current use of immunoglobulin replacement	7 (13.2%)
Chemotherapy	
History of cytotoxic chemotherapy	14 (26.4%)
Current use of cytotoxic chemotherapy	6 (11.3%)
Immunotherapy	
Current use of immunotherapy	5 (9.4%)
History of immunotherapy	9 (16.9%)
Endocrine therapy	
Current use of endocrine therapy	7 (13.2%)
Autologous hematopoietic stem cell transplant	
History of autologous stem cell transplant within past 1 year	3 (5.6%)
History of autologous stem cell transplant >1 year ago	5 (9.4%)
Co-morbidities	
Renal diseases	4 (7.5%)
Autoimmune diseases	2 (3.7%)
Type of vaccine	
Johnson and Johnson	4 (7.5%)
Moderna (mRNA)	9 (16.9%)
Pfizer (mRNA)	40 (75.4%)

patients (50%) who were on cytotoxic chemotherapy, and all five patients (100%) receiving immunotherapy seroconverted.

3.6. Autologous stem cell transplant

Seven of the eight patients (87.5%) who had undergone autologous stem cell transplant, achieved seroconversion with vaccination. Five of these eight patients had more than a year elapse between transplant and the vaccination, while 3 patients had less than a year elapsed. Among these, seven patients who had underlying multiple myeloma and were currently receiving therapy all seroconverted with vaccination. The only post-transplant patient who did not achieve seroconversion had underlying NHL Nolonger receiving therapy and was on immunoglobulin replacement.

3.7. COVID-19 infection

Three of the fifty-three patients (5.6%) had previously documented COVID-19 infection before enrolling in the study and receiving the vaccination for COVID-19. All three patients had elevated spike protein IgG titers at baseline and demonstrated a

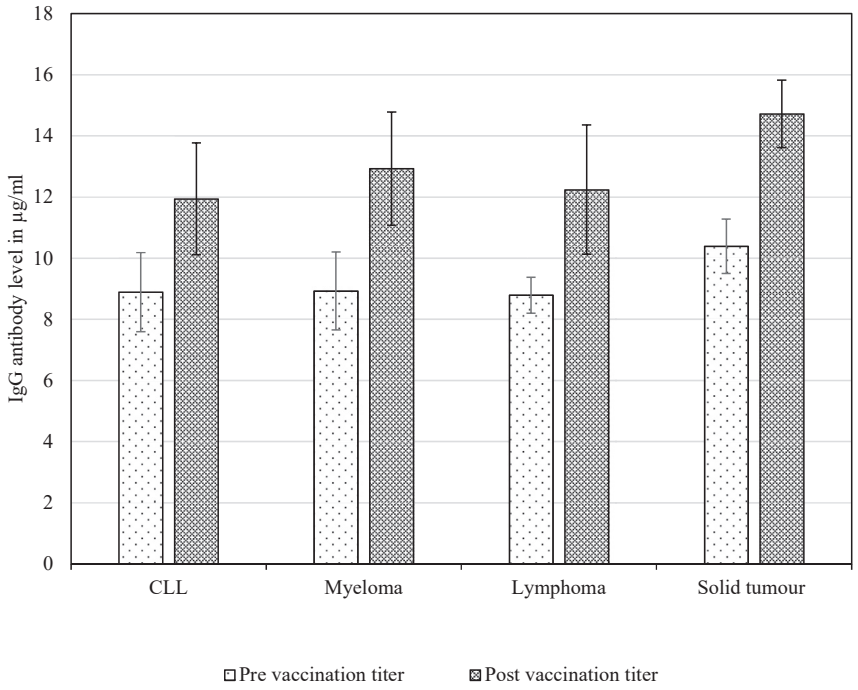
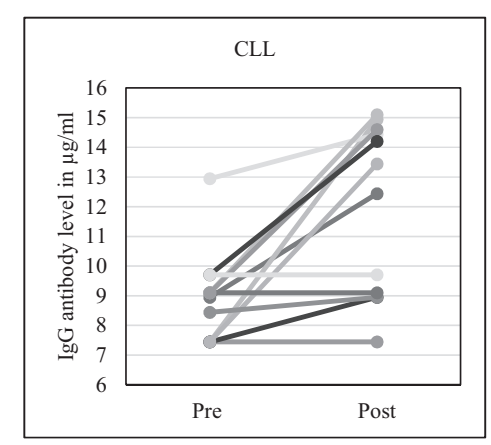


Fig. 1. Bar-graph of pre-and post-vaccination titer (mean and CI) in study patients with various malignancy.



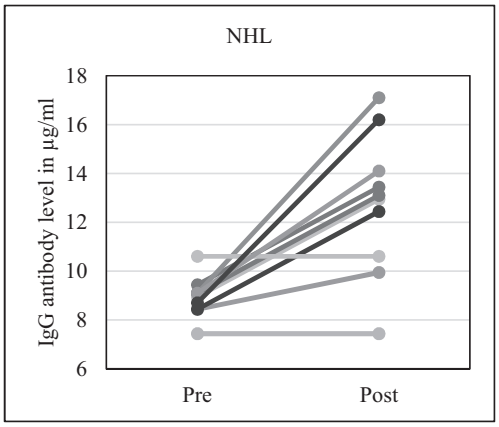
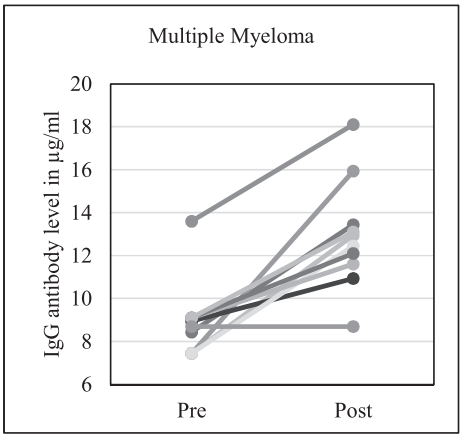


Fig. 2 Line graph of pre-and post-vaccination titer for different types of malignancy in the study population.



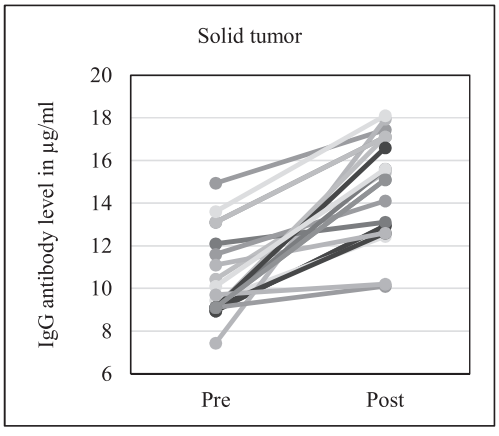


Fig. 2. (continued).

Table 3. Individual patient titers.

	Gender	Age	Ethnicity	History of cancer directed therapy	Current use of cancer directed therapy	History of Rituximab therapy	History of ASCT	Current use of IVIG	Type of vaccine received	Pre- titer#	Post- titer ##
CLL											
1	M	58	C	No	No	No	No	No	Pfizer	8.94	12.44
2	F	74	C	No	No	No	No	No	Moderna	7.44	14.94
3	M	82	C	Yes	Yes	Yes	No	No	Pfizer	7.44	7.44
4	M	68	C	No	No	No	No	No	Pfizer	7.44	8.94
5	F	75	C	No	No	Yes	No	No	Moderna	12.94	14.44
6	M	88	AA	No	No	Yes	No	No	Pfizer	7.44	13.44
7	F	64	C	Yes	Yes	Yes	No	Yes	Pfizer	8.44	8.94
8	F	63	C	Yes	Yes	No	No	No	Pfizer	9.1	9.1
9	F*	85	C	No	No	No	No	No	Pfizer	9.1	15.1
10	F	68	C	No	No	No	No	Yes	Pfizer	9.1	14.6
11	M	58	C	No	No	No	No	Yes	Pfizer	9.7	14.2
12	M	70	C	No	No	No	No	Yes	Pfizer	9.7	9.7
NHL											
13	M	29	C	Yes	Yes	No	No	No	Pfizer	9.44	13.44
14	M	59	C	No	No	No	No	No	Pfizer	8.94	12.94
15	F	73	C	No	No	Yes	No	No	Janssen	8.44	9.94
16	F	55	C	No	No	Yes	No	No	Moderna	8.44	12.44
17	F	59	C	No	No	Yes	No	No	Pfizer	7.44	7.44
18	M	65	C	No	No	Yes	No	No	Moderna	7.44	7.44
19	F	75	C	No	No	Yes	No	Yes	Pfizer	9.1	17.1
20	F	69	AA	No	No	Yes	No	No	Moderna	9.1	13.1
21	M	66	C	No	No	Yes	Yes	Yes	Pfizer	10.6	10.6
22	F	76	C	No	No	Yes	No	No	Pfizer	9.1	14.1
23	F	61	C	No	No	Yes	No	Yes	Pfizer	8.7	16.2
MM											
24	M	56	C	Yes	Yes	No	Yes	No	Pfizer	8.44	13.44
25	M	59	C	Yes	Yes	No	Yes	No	Pfizer	7.44	12.94
26	F	62	C	Yes	Yes	No	Yes	No	Pfizer	7.44	15.94
27	M	75	AA	Yes	Yes	No	No	No	Pfizer	8.94	10.94
28	F	55	C	Yes	Yes	No	Yes	No	Moderna	7.44	12.44
29	M	59	C	Yes	Yes	No	Yes	No	Moderna	9.1	11.6
30	F	61	AA	Yes	Yes	No	Yes	No	Pfizer	13.6	18.1
31	M	67	C	No	No	No	No	No	Pfizer	9.1	12.1
32	M	63	C	Yes	Yes	No	Yes	No	Pfizer	9.1	13.1
33	M	64	C	Yes	Yes	No	No	No	Pfizer	8.7	8.7
Solid Organ Malignancy											
34	F	59	C	No	No	No	No	No	Pfizer	8.94	12.94
35	F	54	C	Yes	Yes	No	No	No	Pfizer	10.44	15.44
36	M	93	C	Yes	Yes	No	No	No	Pfizer	14.94	17.44
37	F	58	C	No	No	No	No	No	Pfizer	8.94	12.94
38	F	43	C	Yes	Yes	No	No	No	Pfizer	9.44	12.44
39	M	60	C	Yes	Yes	No	No	No	Moderna	7.44	17.94

40	F	44	C	Yes	Yes	No	No	No	Janssen	13.1	17.1
41	M	47	O	Yes	Yes	No	No	No	Pfizer	12.1	13.1
42	F	36	C	Yes	Yes	No	No	No	Pfizer	13.1	17.1
43	F	58	C	Yes	Yes	No	No	No	Pfizer	11.6	14.1
44	F	83	C	Yes	Yes	No	No	No	Pfizer	9.1	12.6
45	F	60	AA	Yes	Yes	No	No	No	Pfizer	13.6	18.1
46	M	54	AA	Yes	Yes	No	No	No	Pfizer	11.1	12.6
47	F	39	C	No	Yes	No	No	No	Moderna	9.1	15.1
48	F	47	AA	Yes	Yes	No	No	No	Pfizer	9.1	15.6
49	F	64	C	Yes	Yes	No	No	No	Pfizer	9.1	17.1
50	M	76	C	Yes	Yes	No	No	No	Janssen	9.1	10.1
51	F	27	C	Yes	Yes	No	No	No	Pfizer	9.1	16.6
52	F	59	C	Yes	Yes	No	No	No	Pfizer	10.1	15.6
53	M	65	C	Yes	Yes	No	No	No	Janssen	9.7	10.2

CLL= Chronic lymphocytic leukemia, NHL= Non-Hodgkin's lymphoma, MM = Multiple myeloma, M = Male, F= Female, C= Caucasian, AA = African American, O= Other race/not specified, BMT = autologous hematopoietic stem cell transplant, * Patient had both CLL and breast cancer, # baseline titers of antibodies to COVID- 19 spike protein in log2, ## titers of antibodies to COVID- 19 spike protein in log2, 2 weeks after second dose of BNT162b2 (Pfizer) and mRNA-1273 (Moderna) vaccine or first dose of JNJ-78436735 (Janssen) and J vaccine. Cancer directed therapy = chemotherapy/immunotherapy.

fourfold increase in titers with vaccination, compatible with seroconversion. Based on a detailed chart review, none of the patients developed symptoms of COVID-19 or had a positive COVID-19 PCR during the study period (March 8, 2021, and June 1, 2021).

3.8. Response based on administered vaccine

The majority of patients (n = 40, 75.5%) received vaccination with the BNT162b2 vaccine. Thirty of these 40 patients (75%) seroconverted with vaccination. Among the 10 patients (25%) who did not respond to vaccination, five had CLL, one had MM, two had NHL, and two patients had a solid organ malignancy. Four of the ten patients (40%) who did not respond were actively receiving therapy.

Seven out of nine (77.77%) of our patients who received the MRNA-1273 vaccine achieved seroconversion. Of the two patients (22.2%) who did not seroconvert with vaccination, one had a history of NHL and the other of CLL, and neither were actively receiving therapy.

Seroconversion occurred in only one of the four (25%) patients who received the JNJ-78436735 vaccine. Among the patients who did not respond, one had NHL, not on active treatment, and two had solid organ malignancies, one receiving cytotoxic chemotherapy and the other receiving immunotherapy.

3.9. Controls

All 21 healthy subjects (controls) demonstrated robust IgG titers against SARS-CoV-2 Spike (S) protein. Only post-immunization titers were measured for the controls.

3.10. Adverse effects

Injection site soreness was the most frequently reported side effect of vaccination (54.7% and 61.2% of patients after the first and second dose respectively) (Fig. 3). The other commonly reported side effects after the first and second dose of vaccination were fatigue (3.6% and 22.4%), headache (5.66 and 12.2%), myalgias (1.8% and 12.2%), fever (1 and 10%), and local site rash (1.8% and 2.0% respectively). Only three patients considered their side effects severe and one of these had to be evaluated in the emergency department due to fever. The only severe side effect occurred in a patient with solid organ malignancy who developed Parsonage-Turner syndrome after the JNJ-78436735 vaccine.

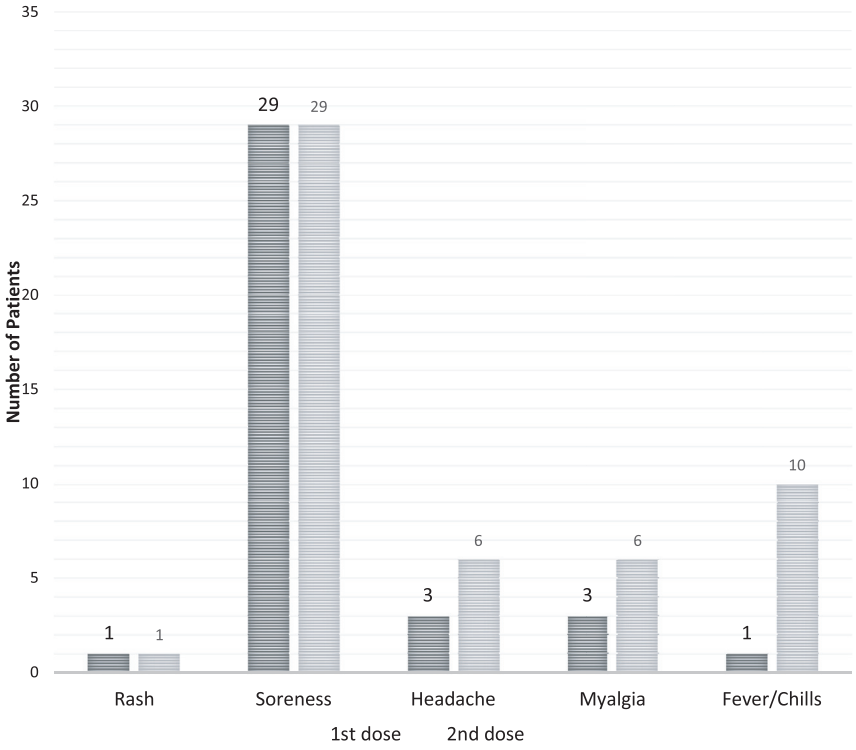


Fig. 3. Bar-graph showing percentage of adverse reactions after 1st and 2nd dose of vaccination in the study population (N = 53).

4. Discussion

The SARS-CoV-2 pandemic originated in 2019 and has been implicated in over 5 million deaths worldwide. The BNT162b2, MRNA-1273, and JNJ-78436735 vaccines are available in the US via FDA approval or through emergency use authorization. There is developing literature that vaccination may be less effective in patients with hematological and/or solid organ malignancies. We conducted this prospective observational study to assess seroconversion in response to vaccination against COVID-19 in patients with CLL, MM, NHL, or solid organ malignancies using a quantitative assay. Using the same assay, we also assessed immune response in 21 healthy controls, who had Nohistory of malignancy, immunosuppression, or other chronic illnesses.

In our study, patients with CLL were less likely to achieve seroconversion in response to vaccination against COVID-19, even when not actively receiving treatment. Patients currently on or with prior history of rituximab use were less likely to seroconvert (0 out of 1 patient currently on rituximab, and 6 out of 13 patients with a history of rituximab seroconverted). These data are consistent with CLL patients having known humoral dysfunction, even early in the disease and at the time of diagnosis, as evidenced by previous studies showing suboptimal vaccine responses.[6,8,12] A similar study assessing the presence of antibodies after administration of two doses of BNT162b2 mRNA vaccine and ChAdOx1 (Oxford−AstraZeneca COVID-19 vaccine) vaccine in 299 patients with CLL noted antibodies in only 75% of 299 CLL patients.[13] Another study from Israel comparing CLL patients with healthy controls found antibodies in only 39.5% of 167 patients with CLL after receiving the BNT162b2 messenger RNA (mRNA) COVID-19 vaccine.[14] Additionally, rituximab is known to not only deplete pre-B and mature B cells reducing the humoral responses to vaccination but also influence T cell immunity for many months which may again impair immune response.[15,16] Our results are in accordance with a previous retrospective study that showed 67% (14 out of 21) patients with CLL developed anti-COVID-19 antibodies after symptomatic, confirmed COVID-19 infection.[17] This inability to mount an adequate antibody response is likely what leads to patients with CLL having higher mortality due to COVID-19 infection, irrespective of being on active therapy vs wait and watch approach.[18]

Similar to patients with CLL, patients with NHL were also less likely to achieve seroconversion in response to vaccination, even when not actively receiving treatment and when not suffering from hypogammaglobulinemia. A previous study found significantly lower neutralizing antibody titers in

patients with CLL/NHL and Waldenstrom macroglobulinemia (17%) vs controls (32%) after the first dose of the BNT162b2 and CHADOX1 NCOV-19 vaccine.[19]

Similar to patients with CLL/NHL, there are concerns that patients with MM may have a suboptimal response to vaccination against SARS- CoV-2 as well. In our study, patients with multiple myeloma were very likely to demonstrate seroconversion irrespective of being on active chemotherapy or having received an autologous stem cell transplant. This is concordant with a study from the UK which found 9 of the 11 patients (82%) vaccinated within 12 months of autologous HSCT tested positive for SARS-CoV-2 IgG antibodies.[20] The same study also found IgG anti-spike antibodies in 52 (56%) of 93 MM patients after receiving only one dose of either BNT162b2 or ChAdOx1 nCoV-19. Our study contrasts with some other studies which have found a reduced response to vaccination in this population, which may be related to a majority (70%) of our MM patients being status post ASCT which may have restored immune function. A study comparing the presence of neutralizing antibodies after administration of the BNT162b2 vaccine in a geriatric population with multiple myeloma (median age 83 years) versus a control group of similar-aged healthy individuals found significantly lower neutralizing antibody titers in the MM group (20·6% vs 32·5%; $p < 0·01$). Another study reported lower immunogenicity in patients with a history of hematopoietic stem cell transplant.[21,22]

Active chemotherapy may be associated with a reduced response to vaccination. In our study, patients with solid organ malignancies had a much higher response to vaccination as compared to patients with CLL/NHL. This may be due to intact B cell function or recovery in immune function between cycles of chemotherapy. This is in line with the findings of a study from the UK in which 18 (95%) of 19 patients with solid cancer had seroconversion after two doses of the BNT162b2 vaccine.[23] A large study including 545 patients with solid organ malignancy found lower antibody concentrations in patients who received chemotherapy in the past 12 months.[22]

Vaccination against COVID-19 was well tolerated in our patient population, similar to what has been reported in the general population and other studies looking at patients with hematologic malignancy. While adverse effects were more common with the second dose of the BNT162b2 and mRNA-1273 vaccines, most patients only suffered from minor symptoms which did not necessitate medical evaluation. Only one patient had a prolonged and serious side effect (Parsons Turner syndrome).

Unlike most other studies, we measured baseline antibody titers prior to vaccination as well. Our study was however limited by the small sample size which precluded a statistical analysis between different patient subpopulations as well as between the different types of vaccines. We have used the generation of antibodies as a surrogate for immunity to SARS-CoV-2, but we did not perform neutralizing assays. We did not follow for other clinical outcomes such as breakthrough infections or the severity of infections. Our study also does not assess T cell response, an important component of immune response to viral antigens. We looked at neutralization of the Wuhan strain of SARS- CoV-2, which may not readily translate into neutralization of the newer strains including the delta and omicron strains, which is the prevalent strain in the US right now. Our study participants are mostly of Caucasian descent and a majority received the BNT162b2 or MRNA-1273 vaccine, therefore, our results may not be representative of patients of non-Caucasian descent and those who received the JNJ-78436735 vaccine.

Our study adds to the body of literature showing that patients with CLL and NHL may not mount an adequate antibody response to vaccination against COVID-19, especially if treated with B cell-depleting agents such as rituximab. The efficacy of additional doses of vaccination in this population needs to be evaluated, as well as other strategies at providing protection to this at-risk population from COVID-19 infection.

Conflict of Interest

Mukul Singal, Sanjana Kalvehalli Kashinath, and Karthik Vadamalai declare No conflicts of interest.

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