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SCIENCE

Reduced Immune Response and Neutralizing Antibody Activity to the SARS-CoV-2 Vaccination in Patients with a History of Solid Organ Transplant

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Keywords: SARS-CoV-2, COVID-19, vaccination, immune response, solid organ transplant, antibodies

Abbreviations: RBD, receptor binding domain; RFUs, relative fluorescence units; RLUs, relative light units; ACE2, angiotensin-converting enzyme 2 protein.

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ABSTRACT

Objective: Three SARS-CoV-2 vaccinations and boosters are available. We determined whether solid organ transplant patients mounted an immune response to the vaccinations and whether the antibodies had neutralizing activity compared to healthcare worker controls and monoclonal gammopathy patients.

Methods: Remnant plasma was obtained from vaccinated solid organ transplant, allogeneic stem cell transplant, monoclonal gammopathy patients, and healthcare worker controls. Samples positive on a SARS-CoV-2 IgG assay (detects spike protein and nucleocapsid) were run on a SARS-CoV-2 in vitro neutralizing antibody assay and a nucleocapsid-specific SARS-CoV-2 IgG assay.

Results: Only 25% of solid organ transplant patients produced antibodies to SARS-CoV-2 vaccination. Of these, 90% had neutralizing activity against wild type virus, but reduced activity to the variants compared to monoclonal gammopathy patients and healthcare worker controls, particularly the delta variant, for which only 50% had neutralizing antibody activity.

Conclusion: Solid organ transplant patients should consider protecting themselves against future SARS-CoV-2 infection.

As of March 3, 2022, the SARS-CoV-2 virus has infected over 441 million people worldwide resulting in >5.9 million deaths.[1] Along with masking and social distancing measures, development, approval, and implementation of vaccines is key to stopping the further spread of highly infectious viral infections. To date, the Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccinations were given full US Food and Drug Administration approval on August 23, 2021, and January 31, 2022, respectively. They are both 2-dose vaccines based on mRNA technology. The Johnson and Johnson Janssen vaccine (JNJ-78436735) was given emergency use authorization on February 27, 2021, and is based on a modified adenovirus vector.

Patients who undergo a solid organ or stem cell transplant at any stage of life are required to take medications that suppress the immune system to prevent rejection of the transplanted organ or cells. However, this leaves the patients vulnerable to infection. From a study in the United Kingdom, having a solid organ transplant was associated with greater than 3 times increased risk of death from COVID-19 after adjustment for age.[2] Due to this degree of immunosuppression, organ transplant patients were prioritized to have earlier access to the vaccines should they wish to receive them.

As can be appreciated, immunocompromised individuals may have a lower immune response to vaccinations. In a study of 242 kidney transplant patients, 28 days after the first dose of the Moderna vaccine, only 10.8% of these patients had a positive IgG serology test.[3] This was further confirmed in another study of 436 transplant patients that were a median of 20 days postvaccination with either the Pfizer or Moderna vaccine where only 17% of patients had a detectable antibody response.[4] These authors also found that an antibody response to the vaccines was less likely in transplant patients receiving antimetabolite maintenance immunosuppression therapy (mycophenolate) than in transplant patients receiving other types of therapy.[4] It should be noted, however, that 20 or 28 days may not be a sufficient time period in which to mount an adequate immune response. In a follow-up study, the authors investigated the antibody response in 658 solid organ transplant patients after both doses of the vaccine.[5] They found that 15% of these patients had an antibody response after dose 1 and dose 2 of the vaccine, 46% of these patients had no antibody response after either dose, and 39% had no antibody response after dose 1 but developed an antibody response after dose 2 of the vaccine. The previous finding that patients receiving antimetabolite therapy were less likely to have an immune response to the vaccine was

mirrored in this study, where 57% of patients taking antimetabolites had no antibody response after doses 1 and 2, 35% had no antibody response after dose 1 but developed one after dose 2, and 8% of patients had an antibody response after dose 1 and dose 2.[5]

In a liver transplant–specific study of 161 patients, it was found that antibodies were detectable in 34% of patients after dose 1 (median of 21 days postdose) and 81% after dose 2 at a median of 30 days after the dose and that 39% of patients receiving 2 vaccine doses on antimetabolite therapy vs 5% not on antimetabolite therapy were nonresponders.[6] A later study investigated B-cell and T-cell responses in 16 solid organ transplant patients vs 23 immunocompetent controls and found that only 37% of solid organ transplant patients vs 100% of immunocompetent controls developed anti-SARS-CoV2 IgG antibodies to the spike protein.[7] Further, only 56% of transplant patients had a detectable T-cell response.[7]

In a previous study of 93 multiple myeloma patients, it was found that 56% had a positive SARS-CoV-2 IgG spike protein antibody response after the first dose of either the Pfizer or Oxford-AstraZeneca (AZD1222; viral vector vaccine) vaccines.[8] In another study,[9] it was found that patients with a history of monoclonal gammopathy had a similar antibody response to the Pfizer, Moderna, and Janssen SARS-CoV-2 vaccines as healthcare worker controls. Therefore, the objective of this study was to investigate the SARS-CoV-2 IgG antibody response in patients who had a history of solid organ or stem cell transplant. Further, this study aimed to determine whether the antibodies that were produced by the transplant patients and patients with a history of monoclonal gammopathy had neutralizing activity towards the different strains of the virus in vitro compared to healthcare worker controls.

Materials and Methods

Patient Samples

Institutional review board approval from the University of California San Francisco was obtained for this study. Medical records were reviewed for patients who had laboratory orders placed for tacrolimus, everolimus, sirolimus, and cyclosporine in April and May 2021. If these patients had received either both doses of a SARS-CoV-2 Pfizer or Moderna vaccination or the single dose of the Janssen vaccination and had a medical history of either solid organ or allogeneic stem cell transplant, they were included in this study. Remnant plasma samples sent to the laboratory for routine clinical testing for these patients were retrieved and stored frozen at −20°C (n = 40).

Remnant serum samples from patients with a history of monoclonal gammopathy (n = 12) that had a SARS-CoV-2 vaccination and had a positive SARS-CoV-2 IgG response from the assay described below that detects antibodies against both the spike protein and nucleocapsid were obtained and used as a disease control group. Additional information regarding these patients has been described.[9] Written consent was not required, as remnant samples sent to the laboratory for routine patient care were used for this study.

Healthcare worker controls (n = 20) from Zuckerberg San Francisco General Hospital were recruited and blood samples were drawn (gold top tubes). Written consent was obtained from all subjects. The date(s) of vaccination and type of vaccine received was self-reported.

SARS-CoV-2 IgG Antibody Assay

The Pylon 3D automated immunoassay system was used to quantitatively measure IgG antibodies as previously described[10] on the residual plasma samples retained from the transplant patients. Briefly, this assay is a sandwich-based assay. Fifteen microliters of plasma was mixed with 105 µL diluent in the sample well. The probe, coated with Protein G targeting IgG, was immersed in the sample well for 360 seconds, followed by a wash sequence. The probe was then transferred to a well containing biotinylated SARS-CoV-2 spike receptor binding domain (RBD) (Arg319-Phe541) for a 180 second incubation. The biotinylated RBD binds SARS-CoV-2 specific IgG. Following a wash sequence, the probe was then incubated with a Cy5-streptavidin (Cy5-SA) polysaccharide conjugate reagent for 30 seconds followed by a wash sequence. Fluorescence signal from the bound Cy5-SA on the probe tip was then measured. This assay detects both the nucleocapsid and spike protein of SARS-CoV-2 and therefore cannot differentiate between antibodies produced as a result of COVID-19 infection or those produced due to vaccination. The quantitative assay produces a result of relative fluorescence units (RFUs), and a cutoff of 50 RFUs was considered as positive.[10] RFUs are determined for patient samples based on comparison with a calibration curve ranging from 1 µg/mL to 300 µg/mL of SARS-CoV-2 human IgG standard spiked into negative human serum. The assay is linear to 300 µg/mL corresponding to 6976 RFUs. Therefore, the higher the number of RFUs, the greater the antibody response.

SARS-CoV-2 IgG Nucleocapsid Antibody Assay

The samples from transplant patients that were positive on the SARS-CoV-2 IgG antibody assay described above were run on a chemiluminescent microparticle immunoassay designed to detect only antibodies against the nucleocapsid protein of the virus on the Architect i2000 instrument (Abbott Laboratories). This assay uses SARS-CoV-2 antigen coated paramagnetic microparticles that are incubated with the patient sample, allowing the IgG antibodies in the sample to bind to the antigen. There is a washing step: anti-human IgG acridinium-labeled conjugate is added, creating a reaction mixture, which is incubated, and the addition of a pre-trigger and trigger solution cause a chemiluminescent reaction, which is measured in relative light units (RLUs). There is a direct relationship between the amount of IgG antibodies in the patient sample and the RLUs detected. The result is reported as an index based on dividing the sample result by the calibrator result to determine whether a patient sample is positive or negative for the antibodies. The cut-off index for positivity is ≥1.4 S/C (sample result divided by calibrator result).

SARS-CoV-2 In Vitro Neutralizing Antibody Assay

The Pylon neutralizing antibody assay is a competitive binding assay. Twenty-six microliters of plasma was mixed with 104 µL of assay buffer containing biotinylated recombinant angiotensin-converting enzyme 2 protein (ACE2) in the sample well. The probe, coated with SARS-CoV-2 spike RBD (Arg319-Phe541), was immersed in the sample well and incubated for 720 seconds. The biotinylated ACE2 competes with any neutralizing antibody present in the sample to bind the immobilized RBD on the probe. Following a wash sequence, the probe was then incubated with streptavidin conjugated to cyanine 5 (Cy5-SA) for 30 seconds, followed by a wash sequence. Fluorescence signal from the bound Cy5-SA on the probe tip was measured.

The amount of fluorescence signal measured is inversely proportional to the amount of neutralizing antibody present in the sample. The result output is a ratio index value (B/B_0), where B is the fluorescence signal measurement for the sample and B_0 is a preestablished value determined by testing negative pre-COVID-19 sera and is the fluorescent measurement for maximum binding. The cutoff index value used in this study was 0.73 using 30 pre-COVID-19 control serum samples. Any index value above 0.73 was negative (–) for neutralizing antibody and any below 0.73 was positive (+); the lower the signal, the more neutralizing antibody activity in the patient sample. Neutralizing antibody activity against the following variants of SARS-CoV2 was investigated: D614G (original variant), B.1.1.7 (alpha variant), B.1.351 (beta variant), B.1.1.28 (gamma variant) and B.1.617 (delta variant). The between-batch imprecision of this assay was ≤10% for all variants. All patient samples that had a positive IgG antibody assay result were used in the neutralizing antibody assay.

Data Analysis

Data analysis was performed in Excel (Microsoft). For each of the variants, a 2 × 2 χ^2 test was performed comparing the positive neutralizing antibody assay results between the combined group of patients with a history of monoclonal gammopathy and healthcare worker controls vs the solid organ transplant patients (that were positive in the SARS-CoV-2 IgG antibody assay) using MedCalc v.19.6.4. A *P* value of < .05 was deemed significant.

Results

Study Population

The demographic information for the 40 transplant patients included in this study can be seen in **TABLE 1**. Out of 40 patients, 13 were female and 27 were male with a mean and median age of 67 and 69 years, respectively (range, 28–87 years). Fifteen of the patients had previously had a kidney transplant, 8 had a liver transplant, 9 had a lung transplant (3 of which were bilateral), 5 had a heart transplant, 2 had allogeneic stem cell transplants, and 1 patient had a heart and lung transplant. Mean and median time since transplant was 6.8 and 5.8 years, respectively (range, 0.5–22.8 years). Twenty-five patients received the Pfizer vaccine, 13 patients received the Moderna vaccine, and 2 patients received the Janssen vaccine. The mean and median time since the first or only dose of the vaccine were 71 and 73 days, respectively (range, 14–100 days).

Demographic information for the 12 patients with a history of monoclonal gammopathy run on the SARS-CoV-2 neutralizing antibody assay and included in this study can be seen in **TABLE 2** and from the healthcare worker controls in **TABLE 3**.

SARS-CoV-2 IgG Antibodies in Solid Organ and Stem Cell Transplant Patients

Of the 40 transplant patients included in this study, only 10 had a positive SARS-CoV-2 IgG antibody test (25%) (**TABLE 4**). Of the 10 patients that were positive, 2 had a heart transplant, 1 had a heart and lung transplant, 3 had a kidney transplant, 3 had a liver transplant, and 1 had a lung transplant. Of the 3 patients that had a SARS-CoV-2 IgG result of >500 RFUs, all of them had liver transplants. The liver transplant patient with the highest SARS-CoV-2 IgG result was only receiving tacrolimus as immunosuppressive therapy and it had been 22.8 years since the transplant. The other 2 liver transplant patients with RFUs of >500 were taking mycophenolate and tacrolimus, and sirolimus and tacrolimus, respectively, and it had been 2.2 and 8.1 years since their respective transplants. Neither of the two patients who had undergone allogeneic stem cell transplant had a positive SARS-CoV-2 IgG antibody test.

The SARS-CoV-2 IgG RFUs showed a positive trend with increasing time since second dose of the vaccination in the 40 transplant patients (**FIGURE 1**). Increasing age had a slightly positive trend with RFUs in the 40 transplant patients and 20 healthcare worker controls, but a slightly negative trend with RFUs in the 12 patients with a history of monoclonal gammopathy (**FIGURE 2**). Further, the SARS-CoV-2 IgG RFUs also showed a slight positive trend with days since second dose of the Moderna vaccine and the Pfizer vaccine in the transplant patients (**FIGURE 3**).

SARS-CoV-2 IgG Nucleocapsid Antibody Assay

Of the 10 patients that had a positive antibody result on the assay described above, 9 had sufficient sample remaining to be tested on a SARS-CoV-2 IgG assay that only detected antibodies to the nucleocapsid protein. All 9 samples were negative on this assay, indicating that the antibody response seen in the previously described assay was directed at the spike protein. This result could indicate that the antibodies were from the vaccine and not from prior infection, or that the sample was taken from these patients after sufficient time had passed from SARS-CoV-2 infection that the nucleocapsid antibody titer had decreased. For the 1 patient that did not have sufficient sample remaining to perform this assay, chart review did not indicate a prior COVID-19 infection.

In Vitro Neutralizing Antibody Assay

The samples from solid organ transplant patients (n = 10), patients with a history of monoclonal gammopathy (n = 12) and from 20 healthcare worker controls that had detectable SARS-CoV2 IgG antibodies were run on the in vitro surrogate neutralizing antibody assay. A cutoff of 0.73 was used to determine whether the sample was positive for neutralizing antibodies, with the lower the number, the more neutralizing activity that was observed. The healthcare worker control samples all had neutralizing antibody activity for the original variant of the virus and for the other variants, but they were less effective for these other variants (**TABLE 5**). The patient samples from patients with a history of monoclonal gammopathy all had neutralizing antibody activity for the original variant of the virus, the alpha variant (B.1.1.7) and the delta variant (B.1.617). With one exception, 11 out of 12 patients (92%) with monoclonal gammopathy had neutralizing antibody activity to all of the variants (**TABLE 6**). The one exception (8%) had no neutralizing antibody activity against either the beta or gamma variants (B.1.351 and B.1.1.28, respectively) (**TABLE 6**). Nine out of 10 solid organ transplant patient samples had neutralizing antibody activity for the original variant of the virus (90%). Two out of 10 patient samples had no neutralizing antibody activity for the alpha variant (B.1.1.7; 20%), 3 out of 10 patient samples had no neutralizing antibody activity for the beta variant (B.1.351; 30%), 3 out of 10 patients had no neutralizing antibody activity for the gamma variant (B.1.1.28; 30%), and 5 out of 10 patients had no neutralizing antibody activity for the delta variant (B.1.617; 50%) (**TABLE 7**).

TABLE 1. Demographic Information for the 40 Solid Organ or Allogenic Stem Cell Transplant Patients Included in the Study

Patient	Age, y/Sex	Days Since Dose 1, 2	Vaccine	Transplant Type	Years Since Transplant	Current Immunosuppressant Medications
1	67/M	67, 40	P	Heart	2.1	Everolimus, tacrolimus
2	69/F	79, 58	P	Heart	8.0	Mycophenolate, tacrolimus
3	69/M	71, 42	P	Heart	4.4	Everolimus, mycophenolate, tacrolimus
4	50/F	48, 20	M	Heart	12.7	Mycophenolate, tacrolimus
5	61/M	67, 41	M	Heart	2.8	Mycophenolate, tacrolimus
6	28/F	50, 29	P	Heart and lung	4.8	Mycophenolate, prednisone, tacrolimus
7	78/F	56, 28	M	Kidney	9.0	Azothioprine, prednisone, tacrolimus
8	68/M	68, 47	P	Kidney	2.9	Mycophenolate, prednisone, tacrolimus
9	71/M	64, 25	P	Kidney	4.3	Mycophenolate, prednisone, tacrolimus
10	45/F	76, 23	P	Kidney	0.7	Mycophenolate, prednisone, tacrolimus
11	71/M	77, 55	P	Kidney	6.0	Mycophenolate, prednisone, tacrolimus
12	87/M	93, 72	P	Kidney	7.1	Mycophenolate, tacrolimus
13	57/M	14, NA	J	Kidney	3.6	Mycophenolate, prednisone, tacrolimus
14	68/M	76, 48	M	Kidney	7.7	Mycophenolate, prednisone, tacrolimus
15	67/M	74, 53	P	Kidney	18.0	Mycophenolate, prednisone, tacrolimus
16	72/F	72, 47	P	Kidney	0.8	Mycophenolate, prednisone, tacrolimus
17	70/F	73, 45	P	Kidney	3.6	Mycophenolate, prednisone, tacrolimus
18	78/F	93, 65	M	Kidney	8.4	Prednisone, tacrolimus
19	74/M	100, 72	M	Kidney	0.9	Mycophenolate, prednisone, tacrolimus
20	68/M	85, 63	P	Kidney	4.2	Mycophenolate, tacrolimus
21	63/M	61, 40	P	Kidney	11.6	Mycophenolate, prednisone, tacrolimus
22	81/M	93, 65	M	Liver	22.8	Tacrolimus
23	69/F	66, 38	M	Liver	8.1	Sirolimus, tacrolimus
24	73/M	97, 65	M	Liver	7.4	Mycophenolate, prednisone, tacrolimus
25	66/M	73, 52	P	Liver	3.1	Mycophenolate, tacrolimus
26	66/F	71, 30	P	Liver	8.4	Mycophenolate, tacrolimus
27	67/M	73, 44	M	Liver	2.2	Mycophenolate, tacrolimus
28	60/M	44, NA	J	Liver	4.9	Mycophenolate, tacrolimus
29	74/F	62, 35	P	Liver	19.4	Prednisone, tacrolimus
30	71/M	67, 25	P	Lung	5.7	Mycophenolate, prednisone, tacrolimus
31	73/F	82, 61	P	Lung	12.6	Everolimus, mycophenolate, prednisone, tacrolimus
32	56/F	37, 16	P	Lung	13.8	Mycophenolate, prednisone, tacrolimus
33	58/M	71, 47	P	Lung	8.7	Prednisone, sirolimus, tacrolimus
34	55/M	44, 23	P	Lung	8.1	Mycophenolate, prednisone, tacrolimus
35	75/M	93, 65	M	Lung	6.1	Mycophenolate, prednisone, tacrolimus
36	74/M	69, 30	P	Lung, bilateral	6.1	Everolimus, prednisone, tacrolimus
37	73/M	89, 60	M	Lung, bilateral	3.5	Mycophenolate, prednisone, tacrolimus
38	69/M	78, 50	P	Lung, bilateral	3.7	Everolimus, mycophenolate, prednisone, tacrolimus
39	72/M	82, 60	P	Stem cell, allogeneic	2.8	Prednisone, tacrolimus
40	69/M	85, 56	M	Stem cell, allogeneic	0.5	Tacrolimus

J, Janssen vaccine; M, Moderna vaccine; NA, not applicable; P, Pfizer vaccine.

A 2 × 2 χ^2 test was performed comparing the percentage of positive neutralizing antibody responses in the combined healthcare worker controls and patients with a history of monoclonal gammopathy group vs the solid organ transplant patients (**TABLE 8**). The solid organ transplant patients had similar neutralizing antibody activity to the original SARS-CoV-2 strain ($P = .0736$), but a significantly lower neutralizing antibody activity to the alpha ($P = .0104$), beta ($P = .0125$), and gamma ($P = .0125$), and particularly the delta variant ($P < .0001$) of SARS-CoV-2.

TABLE 2. Demographic Information for Patients with a History of Monoclonal Gammopathy Run on the SARS-CoV-2 Neutralizing Antibody Assay

Patient	Age, y/Sex	Days Since Dose 1, 2	Vaccine	Diagnosis
1	66/M	70, 37	P	MGUS
2	76/M	47, 20	M	MM not in remission
3	66/M	60, 32	M	SMM
4	49/F	66, 38	M	MM in remission with hypogammaglobulinemia
5	73/M	69, 41	M	MGUS
6	58/M	52, 21	M	MM in remission with hypogammaglobulinemia
7	38/M	19, NA	J	MGUS
8	66/F	60, 42	M	MGUS
9	60/F	71, 42	M	MGUS
10	66/M	73, 53	P	Free light chain amyloidosis
11	79/M	44, 16	M	MGUS
12	67/M	33, 5	M	MM not in remission

J, Janssen vaccine; M, Moderna vaccine; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; NA, not applicable; P, Pfizer vaccine; SMM, smoldering multiple myeloma.

TABLE 3. Demographic Information for Healthcare Worker Controls Run on the SARS-CoV-2 Neutralizing Antibody Assay

Control	Age, y/Sex	Days Since Dose 1, 2	Vaccine
1	29/F	80, 52	M
2	28/M	57, 29	M
3	36/M	62, 41	P
4	54/F	91, 69	P
5	66/M	51, 30	P
6	41/F	79, 48	M
7	35/F	92, 62	M
8	59/F	52, 24	M
9	36/M	109, 88	P
10	32/F	102, 72	M
11	52/F	108, 87	P
12	39/F	116, 94	P
13	66/F	110, 89	P
14	28/M	89, 67	P
15	47/F	103, 82	P
16	32/F	112, 91	P
17	46/M	114, 93	P
18	46/F	127, 96	P
19	41/M	112, 93	P
20	39/M	115, 94	P

M, Moderna vaccine; P, Pfizer vaccine.

TABLE 4. SARS-CoV-2 IgG Antibody Detection by Transplant Type

Transplant Type	Total No.	No. (%) Positive for COVID IgG
Heart	5	2 (40)
Heart and lung	1	1 (100)
Kidney	15	3 (20)
Liver	8	3 (38)
Lung	9	1 (11)
Allogeneic stem cell	2	0 (0)

Discussion

This study aimed to determine the SARS-CoV-2 IgG antibody response in patients who had a history of solid organ or allogenic stem cell transplant and had received the SARS-CoV-2 vaccination. Only 25% of these patients had a positive SARS-CoV-2 IgG antibody response based on a positive cutoff of 50 RFUs. This is in line with reports in kidney transplant patients and other solid organ transplant patients.[3–7]

Transplant patients need to be maintained on immunosuppressant therapies to prevent rejection of the transplanted organ, but a balance must be maintained between preventing rejection and the side effects

of these medications. Liver transplant patients tend to be maintained on lower levels of immunosuppressants than other solid organ transplant recipients[6] and it is also possible to withdraw immunosuppressant treatment completely in selected patients.[11] This may be a plausible explanation for the increased SARS-CoV-2 IgG antibody response that was observed in liver transplant patients in this study compared to other solid organ transplants. Further, in this study, the majority of patients were receiving mycophenolate. Immunosuppression regimens including mycophenolate have previously been reported to be associated with a reduction in antibody production to the SARS-CoV-2 vaccine in solid organ transplant patients after both the first and second doses of the vaccine.[4,5]

Because the vaccines were designed around the original SARS-CoV-2 spike protein that was detected, the expectation would be that these antibodies would have neutralizing activity towards the original variant, which is what was found in this study of control healthcare workers and patients with a history of monoclonal gammopathy, and to a lesser extent, in solid organ transplant patients. These antibodies produced from the vaccines also seem to have neutralizing activity for the variants in the spike protein in healthcare worker controls and patients with a history of monoclonal gammopathy, and to a significantly lesser degree, in the solid organ transplant patients, for the alpha, beta, and gamma variants but especially for the delta variant (B.1.617), in which only 50% of solid organ transplant patients that

FIGURE 1. Linear regression correlation between relative fluorescence units obtained on the SARS-CoV-2 IgG antibody assay and days since vaccination and dose 2 for solid organ and allogenic stem cell transplant patients. y = 4.9724 x –41.476; R^2 = 0.017.

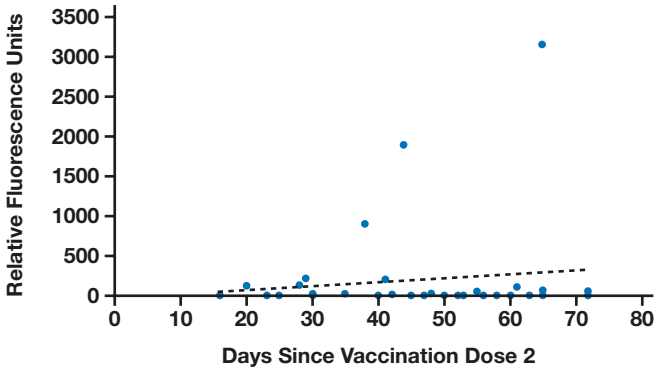

FIGURE 2. Linear regression correlation between relative fluorescence units obtained on the SARS-CoV-2 IgG antibody assay and age of the patient when the sample was collected for solid organ and allogenic stem cell transplant patients (y = 9.2119x –441.28; R^2 = 0.0264) (A), patients with a history of monoclonal gammopathy (y = 15.391x –3848.2; R^2 = 0.0073) (B), and healthcare worker controls (y = 7.3828x –780.74; R^2 = 0.0091) (C).

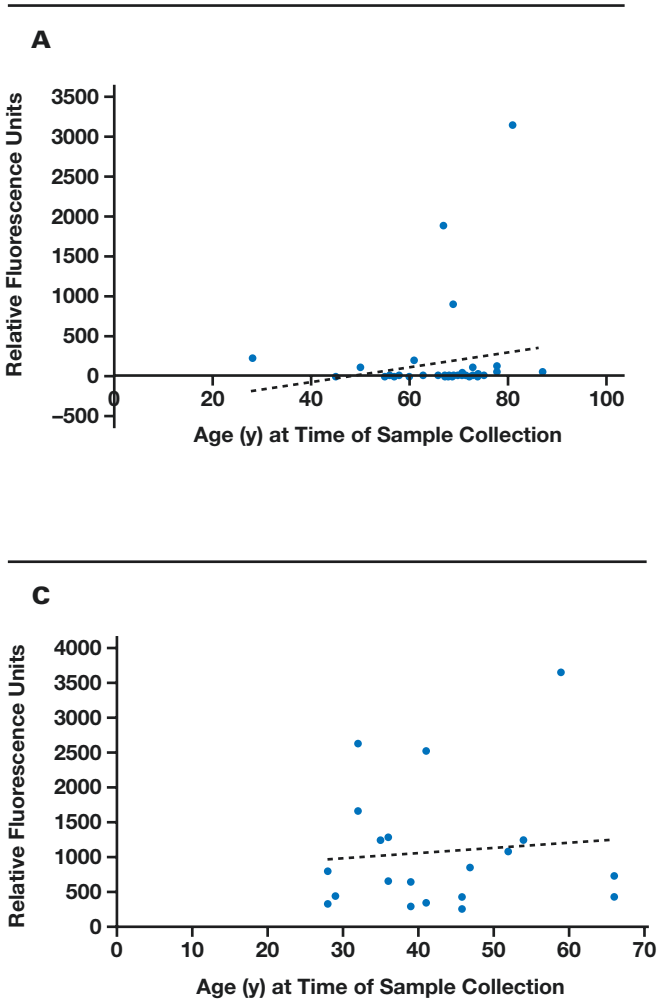

FIGURE 3. Linear regression correlation between relative fluorescence units obtained on the SARS-CoV-2 IgG antibody assay and days since vaccination dose 2 for the Moderna vaccine (y = 3.0557x –344.29; R^2 = 0.0026) (A) and Pfizer vaccine (y = 0.0531x –19.211; R^2 = 0.0003) (B) for solid organ and allogeneic stem cell transplant patients.

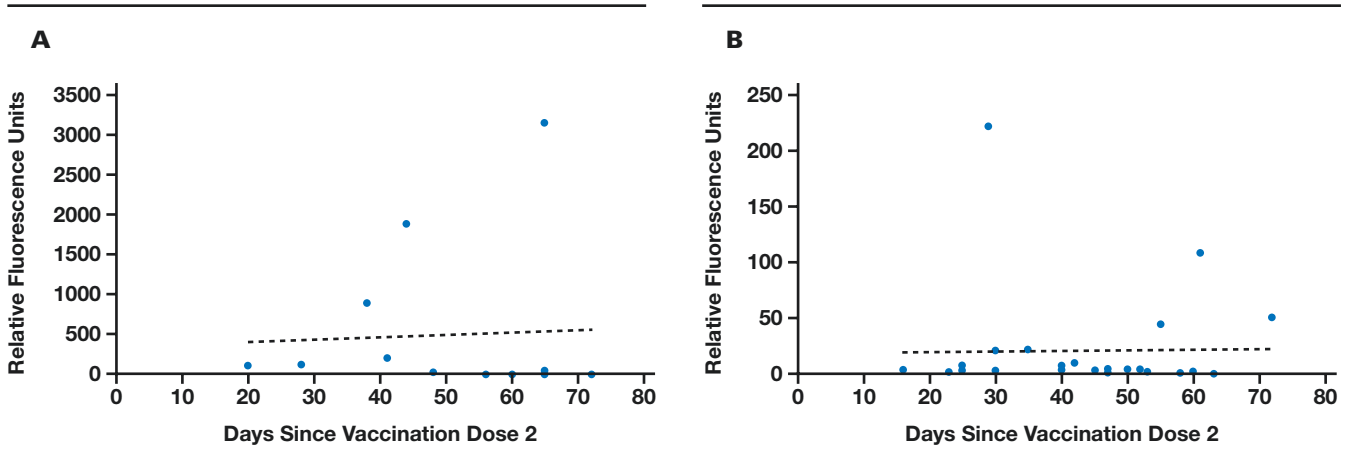

TABLE 5. In Vitro Neutralizing Antibody Activity in Healthcare Worker Controls

Control	Original Variant D614G		Alpha Variant B.1.1.7		Beta Variant B.1.351		Gamma Variant B.1.1.28		Delta Variant B.1.617	
	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)
1	0.01	(+)	0.09	(+)	0.08	(+)	0.06	(+)	0.07	(+)
2	0.02	(+)	0.11	(+)	0.09	(+)	0.09	(+)	0.07	(+)
3	0.08	(+)	0.34	(+)	0.25	(+)	0.24	(+)	0.25	(+)
4	0.07	(+)	0.29	(+)	0.27	(+)	0.24	(+)	0.19	(+)
5	0.17	(+)	0.52	(+)	0.46	(+)	0.43	(+)	0.39	(+)
6	0.01	(+)	0.08	(+)	0.07	(+)	0.07	(+)	0.04	(+)
7	0.03	(+)	0.18	(+)	0.16	(+)	0.19	(+)	0.12	(+)
8	0.01	(+)	0.04	(+)	0.04	(+)	0.04	(+)	0.02	(+)
9	0.17	(+)	0.59	(+)	0.57	(+)	0.51	(+)	0.47	(+)
10	0.01	(+)	0.06	(+)	0.05	(+)	0.06	(+)	0.04	(+)
11	0.14	(+)	0.38	(+)	0.38	(+)	0.37	(+)	0.30	(+)
12	0.41	(+)	0.67	(+)	0.55	(+)	0.55	(+)	0.52	(+)
13	0.32	(+)	0.71	(+)	0.66	(+)	0.65	(+)	0.57	(+)
14	0.13	(+)	0.35	(+)	0.54	(+)	0.42	(+)	0.31	(+)
15	0.06	(+)	0.26	(+)	0.24	(+)	0.25	(+)	0.14	(+)
16	0.03	(+)	0.13	(+)	0.13	(+)	0.12	(+)	0.08	(+)
17	0.10	(+)	0.34	(+)	0.29	(+)	0.29	(+)	0.24	(+)
18	0.33	(+)	0.70	(+)	0.66	(+)	0.67	(+)	0.54	(+)
19	0.20	(+)	0.52	(+)	0.47	(+)	0.46	(+)	0.43	(+)
20	0.19	(+)	0.57	(+)	0.50	(+)	0.48	(+)	0.42	(+)

had a positive antibody response had neutralizing activity towards it. To our knowledge, this is the first study to document this finding, which is particularly relevant as the delta variant was the most fatal SARS-CoV-2 variant in a number of countries around the world. This information should be disseminated to solid organ transplant patients so that they are aware that they may have an attenuated response to the SARS-CoV-2 vaccines and they should continue to employ risk-reduction strategies such as social distancing and wearing masks to protect themselves, as well as obtaining a booster vaccine dose that is available for each type of vaccine and has been shown to illicit an antibody response in solid organ transplant patients who previously had no detectable antibody titers.[12]

There are several limitations to this study, including the very small number of patients included. There is no baseline antibody concentration data from these patients, and there are no data on the SARS-CoV-2 infection history. Further, 1 patient that had a positive antibody response to the SARS-CoV-2 spike protein assay had insufficient sample remaining to be run on the SARS-CoV-2 assay for nucleocapsid-directed antibodies. Although the SARS-CoV-2 IgG RFUs showed a positive trend with increasing time since the second dose of the vaccination as well as

TABLE 6. In Vitro Neutralizing Antibody Activity in Patients with a History of Monoclonal Gammopathy

Patient	Original Variant D614G		Alpha Variant B.1.1.7		Beta Variant B.1.351		Gamma Variant B.1.1.28		Delta Variant B.1.617	
	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)
1	0.07	(+)	0.08	(+)	0.44	(+)	0.45	(+)	0.37	(+)
2	0.15	(+)	0.16	(+)	0.83	(–)	0.90	(–)	0.44	(+)
3	0.03	(+)	0.03	(+)	0.39	(+)	0.37	(+)	0.17	(+)
4	0.06	(+)	0.06	(+)	0.30	(+)	0.34	(+)	0.31	(+)
5	0.01	(+)	0.02	(+)	0.29	(+)	0.27	(+)	0.14	(+)
6	0.03	(+)	0.03	(+)	0.36	(+)	0.34	(+)	0.21	(+)
7	0.01	(+)	0.01	(+)	0.10	(+)	0.09	(+)	0.03	(+)
8	0.00	(+)	0.03	(+)	0.05	(+)	0.04	(+)	0.01	(+)
9	0.01	(+)	0.05	(+)	0.06	(+)	0.06	(+)	0.02	(+)
10	0.01	(+)	0.07	(+)	0.18	(+)	0.15	(+)	0.06	(+)
11	0.00	(+)	0.04	(+)	0.08	(+)	0.08	(+)	0.02	(+)
12	0.01	(+)	0.02	(+)	0.22	(+)	0.21	(+)	0.10	(+)

TABLE 7. In Vitro Neutralizing Antibody Activity in Solid Organ Transplant Patients

Patient	Original Variant D614G		Alpha Variant B.1.1.7		Beta Variant B.1.351		Gamma Variant B.1.1.28		Delta Variant B.1.617	
	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)	Index (B/B0)	Result (+, –)
4	0.57	(+)	0.66	(+)	0.74	(–)	0.80	(–)	0.84	(–)
5	0.29	(+)	0.54	(+)	0.66	(+)	0.70	(+)	0.68	(+)
6	0.38	(+)	0.64	(+)	0.65	(+)	0.31	(+)	0.62	(+)
7	0.43	(+)	0.67	(+)	0.72	(+)	0.68	(+)	0.87	(–)
12	0.40	(+)	0.68	(+)	0.72	(+)	0.80	(–)	0.99	(–)
18	0.99	(–)	0.82	(–)	1.26	(–)	0.43	(+)	0.89	(–)
22	0.02	(+)	0.05	(+)	0.11	(+)	0.13	(+)	0.06	(+)
23	0.64	(+)	0.12	(+)	0.50	(+)	0.40	(+)	0.18	(+)
27	0.02	(+)	0.07	(+)	0.14	(+)	0.11	(+)	0.05	(+)
31	0.65	(+)	0.81	(–)	0.78	(–)	0.77	(–)	0.96	(–)

TABLE 8. 2 × 2 χ^2 Test Comparing the Number of Samples with a Positive Neutralizing Antibody Response to the Different SARS-CoV-2 Variants Between the Healthcare Worker Controls and Monoclonal Gammopathy Patient Group vs the Solid Organ Transplant Group[a]

SARS-CoV-2 Strain	Health Care Worker Controls and Monoclonal Gammopathy Patients (n = 32)	Solid Organ Transplant Patients (n = 10)	*P* Value
Original variant D614G	32 (100)	9 (90)	.0736
Alpha variant B.1.1.7	32 (100)	8 (80)	.0104
Beta variant B.1.351	31 (96.9)	7 (70)	.0125
Gamma variant B.1.1.28	31 (96.9)	7 (70)	.0125
Delta variant B.1.617	32 (100)	5 (50)	<.0001

[a]*Data are given as No. (%).*

with increasing age in the solid organ transplant patients, the number of samples is low and so it is unclear whether these trends would be reproducible in larger data sets.

Conclusions

The majority of solid organ and stem cell transplant patients included in this study did not mount a sufficient immune response against the SARS-CoV-2 vaccinations to produce a positive IgG antibody titer. Further, in those that did have detectable antibodies, they were found to have lower neutralizing activity to all known variants of the SARS-CoV-2 virus compared to both healthcare worker controls and patients with a history of monoclonal gammopathy, most particularly the delta variant (B.1.617). Therefore, it seems prudent that these solid organ and stem cell transplant patients should obtain a third vaccination dose and a booster dose and continue to follow precautions to limit their exposure

to SARS-CoV-2 until herd immunity is achieved, as their response to the vaccinations seems to be attenuated.

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P.P. and M.Z. are employees of ET Healthcare and performed the neutralizing antibody test for which data are included in this article.

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