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ORIGINAL ARTICLE

Infection

Response to and outcomes of the Pfizer BNT162B2 vaccine in hemodialysis patients—A prospective observational study

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Abstract

Introduction: COVID-19 infection is associated with high mortality among hemodialysis patients. Standard vaccine response is generally lower among these patients. The adequate antibody titer response and the outcome of COVID-19 vaccine responders versus non-responders are unknown.

Methods: Hemodialysis patients on maintenance hemodialysis who have received two doses of Pfizer BNT162B2 vaccine were studied. Antibody response was tested after 14 days of the second dose. LIAISON SARS-CoV2 S1/S2 IgG test by DiaSorin (Italy) was used to assess antibody response. Patients were followed between 3 and 7 months after vaccination for COVID-19 infection, hospitalization and death related to COVID-19.

Findings: A total of 138 patients received two doses of Pfizer BNT162B2 vaccine. One hundred and twenty-seven patients had adequate response to the vaccine with IgG level $\geq$ 15 AU/ml versus 11 patients had poor response with IgG level $\leq$ 15 AU/ml. The response was 92% (127/138). Patient with history of prior COVID-19 infection had higher antibody titer mean of 339 $\pm$ 113 versus 157 $\pm$ 140 for patient with no prior history of COVID-19.

Seven patients in both groups had COVID-19 infection post vaccine. Among the responders, five patients had COIVD-19 infection and two were hospitalized. These two patients had lower antibody titer of 23.9 and 75.2 AU/ml. In comparison, three patients who were not hospitalized had higher antibody titer 96.3, 118, and 319 AU/ml, respectively. In the non-responders one patient was hospitalized and one death occurred with rate of infection of 18%.

Discussion: Seropositive patients with low antibody titer might be associated with worse outcome among responders. The ideal antibody titer level among dialysis patient is not known. Also, prior COVID-19 infection is associated with higher response to vaccine with higher antibody titer. All non-responders

did not have prior COVID-19 infection. More research is required to further evaluated protective antibody titer.

KEYWORDS
BNT162B2 vaccine, COVID-19, Hemodialysis, SARS-CoV-2, vaccine

INTRODUCTION

In December 2020, the U.S. Food Drug Agency approved the emergency use of the Pfizer BNT162B2 vaccine for the prevention of COVID-19 in individuals aged 16 and older.[1] This approval was based on a clinical trial that included healthy volunteers.

Hemodialysis patients are considered to be at high risk of infections, especially from COVID-19.[2] These patients have a higher mortality rate than the average population.[3] In addition, patients on hemodialysis have reduced immunogenicity. For example, compared with immunocompetent adults, hemodialysis patients are less likely to have protective levels of antibodies after receiving standard vaccine doses of Hepatitis B.[4] A study by Simon et al.[5] showed that dialysis patients exhibited significantly reduced anti-SARS-CoV-2 antibody seropositivity compared to healthy controls. Among dialysis patients, the reported rate of antibody response to the SARS-CoV-2 mRNA vaccine ranged between 88% and 95%.[6–8] However, the protective effect of the SARS-CoV-2 mRNA vaccine and its outcomes were not examined.

In this descriptive study, we attempt to examine the response to the Pfizer BNT162B2 COVID-19 vaccine and explore the hospitalization and mortality rates of responders compared to non-responders. In addition, we assess the effect of prior COVID-19 infection on vaccine response among hemodialysis patients.

METHODS

Study population

This is a prospective cohort study where patients were randomly selected from five major hemodialysis centers in Kuwait. Adult patients who received two doses of the Pfizer BNT162B2 vaccine were included. The study was conducted between 2nd of January, 2021 to 31st of July, 2021. Patients were screened for fever and COVID-19 symptoms during every dialysis session as part of the national dialysis screening program. Any patient who was suspected of having symptoms of COVID-19 was immediately isolated and subjected to a nasopharyngeal swab followed by a polymerase chain reaction (PCR) test.

Health records and prior COIVD-19 infections

Specific personnel from each dialysis center were assigned to conduct data collection and quality assurance. Each patient's demographic data were collected electronically; this included age, gender, BMI, and hemodialysis parameters from each dialysis center. Follow up data on hospitalizations and mortality were also collected. Prior and prospective COVID-19 swab results were traced using the national COVID-19 registry, which digitally stores all positive COVID-19 cases using the patient's civil identification number. Each patient was asked to show their vaccination card as proof of vaccination.

SARS-CoV2 S1/S2 antibody test

Following ethical approval from the Ministry of Health, all patients consented to have their blood sampled. An average of 4 ml of blood was collected from each patient at the beginning of the scheduled dialysis session. Each sample was centrifuged after collection for 10 min at an RCF (relative centrifugal field) of 3000. The samples were then delivered to the assigned laboratory technician for processing as per DiaSorin guidelines.

To assess immunogenicity and vaccine response, we tested each patient using a LIAISON SARS-CoV2 S1/S2 IgG test (DiaSorin, Italy) at least 14 days after they received their second dose of the Pfizer BNT162B2 vaccine. This test uses chemiluminescence technology for the quantitative determination of anti-S1 and anti-S2 SARS-Cov-2 antibodies in human serum. The test was carried out by experienced staff using a LIAISON XL analyzer. The manufacturer's reported sensitivity and specificity were 97.4% and 98.5%, respectively.[9] In an independent report from the United Kingdom, the LIAISON SARS-CoV2 S1/S2 IgG was compared to five different assays and had a reported specificity of 98%.[10]

The antibody assay concentration was expressed in units of AU/ml, with the assay ranging up to 400 AU/ml. A result of less than 12 AU/ml was considered to be negative, while a result of less than 15 AU/ml was considered to be equivocal. A result is considered positive if the antibody assays were equal to or more than 15 AU/ml.

Statistical methods

The means and standard deviations were calculated for all continuous variables. Percentages were used for categorical variables. A *t* test was used for normally distributed numerical data, while a Mann–Whitney test was used for non-normally distributed data. All descriptive analyses were performed using STATA 17 (*Stata*

TABLE 1 Demographics of all patients presented with responders versus non-responders

Demographics	All patients ($N = 138$)	Responders (IgG ≥ 15) ($N = 127$)	Non-responders (IgG ≤ 15) ($N = 11$)	*p* value
Age (mean)	64 ± 14	63 ± 13	72 ± 14	<0.001
Gender (N)				
Female	68(51%)	60 (47%)	8 (73%)	
Male	70 (49%)	67(53%)	3 (27%)	0.10
Prior vaccine COVID-19 infection	11(8%)	11(9%)	0	0.31
Etiology of ESKD (N)				
Diabetes	94	86	8	
Hypertension	22	20	2	
Chronic interstitial nephritis	1	1	0	
Unknown cause	7	6	1	
Polycystic kidney disease	4	4	0	
Post renal transplant	1	1	0	
Anti-GBM	2	2	0	
Analgesic use	1	1	0	
SLE	2	2	0	
Neurogenic bladder	1	1	0	
Chronic GN	2	1	0	
BMI	28.5 ± 6.9	28.7 ± 6.9	26.3 ± 5.3	<0.0001
Hemodialysis access				
Fistula	66 (48%)	61 (48%)	5 (46%)	
Graft	5 (4%)	4 (3%)	1 (9%)	
Permcath	67 (48%)	62 (49%)	5 (46%)	
KT/V	1.12 ± 0.3	1.12 ± 0.3	1.13 ± 0.4	0.7
Serum albumin (g/L)	35 ± 4.3	35 ± 4.3	36 ± 5.2	0.9
PTH (pg/ml)	59 ± 60	59 ± 60	56 ± 50	0.8
Days between doses	23.4 ± 5.5	23.2 ± 5	25.5 ± 9	0.4
HD vintage (Years)	4.4 ± 3.9	4.3 ± 4	4.8 ± 4	0.8
Diabetes mellitus	103 (75%)	95 (75%)	8 (73%)	0.9
Immunosuppression				
Prednisolone 5 mg	4 (3%)	4 (3%)	0	
Mycophenolic acid	1 (0.7%)	1 (0.8%)	0	
IVIG	1 (0.7%)	1 (0.8%)	0	
Hepatitis C (+ve)	6 (4%)	6 (5%)	0	0.4

Note: For numerical data values presented as mean data ± standard deviation or categorical data number (percentage) comparing responders to non-responders.

Abbreviations: anti-GBM, anti-glomerular basement membrane; chronic GN, chronic glomerulonephritis; COVID-19, coronavirus disease 2019; ESKD, end-stage kidney disease; HD vintage, hemodialysis vintage; IVIG, intravenous immune globulin; PTH, parathyroid hormone; SLE, systemic lupus erythematosus.

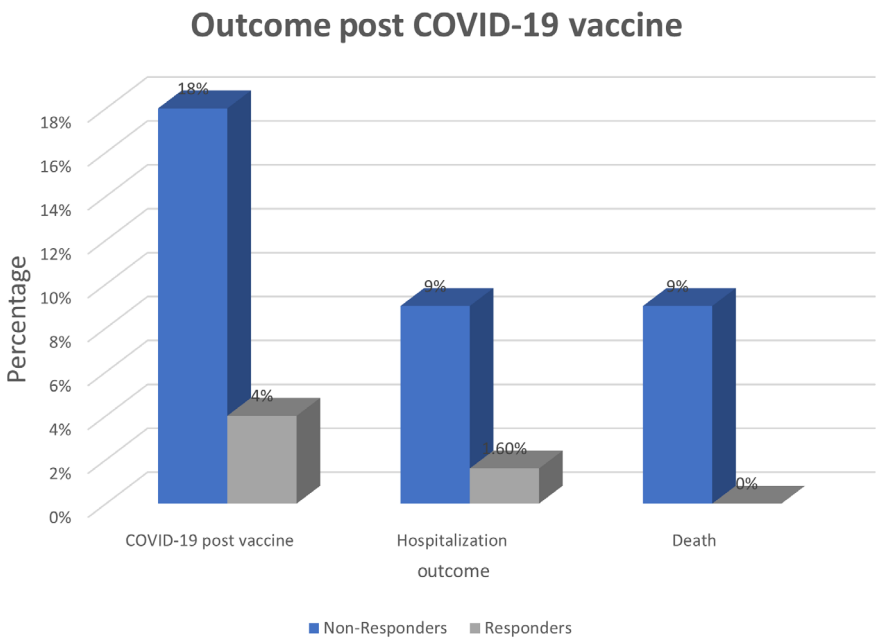

FIGURE 1 Outcome of vaccine responders versus non-responders include COVID-19 infection, hospitalization, and death [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Shows the outcome of patients post vaccine among responders versus non-responders

Outcome	No. patients	COVID-19 infection post vaccine	Hospitalization	Death
Non-responders	11	2 (18%)	1 (9%)	1 (9%)
Responders	127	5 (4%)	2 (1.6%)	0 (0%)

Note: Mean follow up 150 days post vaccine.

TABLE 3 Shows all COVID19 positive patient post vaccine and antibody titer with number of days post vaccine

Outcome	Days post vaccine no.	Antibody titer (AU/ml)	Prior vaccine COVID-19 status
Non-responders (IgG ≤ 15 AU/ml)			
Hospitalized	186	3.8	Negative
Death	173	5.36	Negative
Responders (IgG ≥ 15 AU/ml)			
Hospitalized	158	75.2	Negative
Hospitalized	202	23.9	Negative
Not hospitalized	160	96.3	Negative
Not hospitalized	116	118	Negative
Not hospitalized	131	319	Negative

Statistical Software: Release 17. College Station, TX: StataCorp LLC).

RESULTS

A total of 138 patients received two doses of the Pfizer BNT162B2 vaccine were analyzed. One hundred and twenty-seven patients had an adequate response to the vaccine with an IgG level ≥ 15 AU/ml compared to 11 patients who had a poor response with an IgG level ≤ 15 AU/ml. The response rate to the Pfizer BNT162B2 vaccine among our cohort was 92% (127/138). The mean age of the non-responders was higher than that of the responders (Table 1). 75% of the patients included in the study had diabetes. The mean concentration of serum albumin in both groups was found to be similar at 35 ± 4.3 and 36 ± 5.2 for the responders and non-responders, respectively, with a p value of 0.9. There was no significant difference in the dialysis vintage

TABLE 4 Shows the mean of antibody titer in patients with prior vaccine COIVD-19 infection

COVID-19 status	No. patients	Antibody titer (mean)	Responders	Non-responders
Previous COVID-19 infection	11	339 ± 113	11	0
No prior COVID-19 infection	127	157 ± 140	116	11

Note: *p* value is <0.001 for Antibody titer level for previous COVID-19 infection versus no prior COVID-19 infection.
Abbreviation: COVID-19, coronavirus disease 2019.

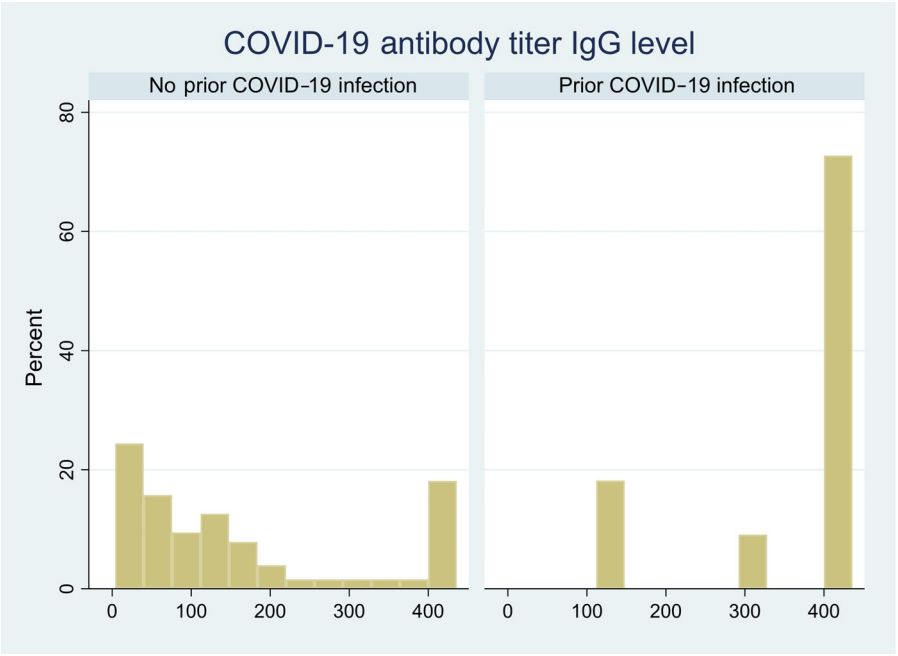

FIGURE 2 COVID-19 antibody titer IgG level 2 weeks after the second dose. No prior COVID-19 infection versus prior COVID-19 infection [Color figure can be viewed at wileyonlinelibrary.com]

between the two groups, with 4.3 ± 4 and 4.8 ± 4 years for responders and non-responders, respectively.

There were only five COVID-19 cases among patients who responded to the vaccine (4%) with two of these cases requiring hospitalization (1.6%); no mortalities were recorded among these patients (Figure 1). However, there were two cases of COVID-19 infection in the group that did not respond to the vaccine (18%), of which one case required hospitalization (9%) and the other died (9%) (Table 2). All post-vaccination COVID-19 infections occurred 100 days (3.3 months) after administration. Patients who required hospitalization had lower SARS-CoV2 S1/S2 IgG antibody levels compared to patients who did not require hospitalization (Table 3).

All patients who had been infected by COVID-19 prior to the vaccination had a better response to the vaccine as demonstrated by their higher mean antibody titer, with a SARS-CoV2 S1/S2 IgG antibody level of 339 ± 113 AU/ml compared to 157 ± 140 AU/ml (*p* value <0.001) in patients without prior exposure to COVID-19 (Table 4). In addition, more of them had SARS-CoV2 S1/S2 IgG antibody levels >400 AU/ml (Figure 2).

DISCUSSION

To ensure that our dialysis patients developed adequate antibody response ideally, we need to measure the neutralizing antibodies. These antibodies inhibit the pathogen's entry and hence reduce the chances of infection. They are considered to be the gold standard.[11] However, this method uses live viruses and is not feasible in every clinical setting as it requires a biosafety level 3 laboratory. In our study, we used the LIAISON SARS-CoV2 S1/S2 IgG test, an assay with a quantitative correlation to neutralizing antibodies. It detects IgG antibodies against the S1 and S2 antigens of SARS-CoV-2. The S1 and S2 antigens are subunits of the spike protein found on SARS-CoV-2. The manufacturer reported that this test was capable of detecting neutralizing antibodies and was 94.4% in agreement with the plaque reduction neutralization test.[9] This test is used to measure titer of neutralizing antibody of the virus. In addition, the LIAISON SARS-CoV2 S1/S2 IgG test was further compared with the surrogate virus neutralization test; they were found to be well-correlated with an *r* value of 0.91.[12] We felt using this test to assess for vaccine response in our patients was

an acceptable surrogate method for assessing the concentration of neutralizing antibodies.

The response rate to the Pfizer BNT162B2 vaccine in our cohort was 92% (127/138). This is consistent with previously reported response rates among dialysis patients[7] but lower than the reported response rates in patients without chronic kidney disease.[13] Although most patients (92%) had an adequate humoral response to the vaccine, it was unclear if this response signaled the presence of a protective effect against COVID-19. In this study, we followed patients for an average of 150 days (5 months) for infections, hospitalizations, or deaths related to COVID-19 complications. Of those who responded to the vaccine, a higher SARS-CoV2 S1/S2 IgG antibody level appears to confer a more protective effect. The two patients who were hospitalized both had lower antibody titers in comparison to the three who did not require hospitalization. It should be mentioned that the threshold for seropositivity provided by the manufacturer was for diagnosis only, and was not indicative of sufficient immune response. Therefore, further studies are required to assess the protective antibody level in hemodialysis patients. Furthermore, these findings support the use of a third dose of the vaccine as booster for these vulnerable patients.

It has been reported that the seroconversion rates in hemodialysis patients who were infected by COVID-19 increase over time.[14] In our study, patients who had been infected by COVID-19 prior to vaccination were associated with a higher antibody titer. This might indicate that vaccination helps to boost natural seroconversion and thus, immunity among hemodialysis patients.

Our study shed the light on the clinical outcomes of the Pfizer BNT162B2 vaccine among hemodialysis patients, despite the small sample size. This study reinforces the importance of COVID-19 vaccination in this high-risk group in reducing hospitalization rates. One important strength of the study is that it was prospective; patients who received the second dose of the vaccination were followed for up to 7 months. In addition, we included all hemodialysis centers in the country. Furthermore, all antibody samples were tested in the same laboratory using the same machine with trained personnel.

An important limitation in our study is that there is no standard antibody that can be used to assess vaccine immunity, and testing for neutralizing antibodies was not feasible. In addition, we did not assess the outcomes with healthy controls. Another limitation of this study is that it did not measure T-cell response to assess for cellular immunity. Clarke et al.[15] have demonstrated that patients who previously had COVID-19 infection with diminished antibody level at 6 months can still have detectable evidence of cellular immunity using T-SPOT SARS-Cov-2 (Oxford Immunotec Ltd).[16] This study has a relatively low sample size, which precludes the use of multivariate analysis.

CONCLUSION

Prior COVID-19 infections were associated with a higher response to the vaccine and higher antibody titers. Each patient that did not respond to the vaccine did not have a prior COVID-19 infection. Among the responders, lower antibody titers appear to be associated with worse outcomes. The ideal antibody titer level among dialysis patients is not known. More research is required to further evaluated adequate.

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CONFLICT OF INTEREST

Dr. Al-Muhaiteeb completed the Baxter—UHN EXPLORE Home Dialysis Fellowship 2015–2016. None of the other authors have any conflict of interest.

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