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Humoral Response to the Third Dose of BNT162b2 COVID-19 Vaccine among Hemodialysis Patients

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Keywords
Hemodialysis patients · COVID-19 vaccine · Third dose · Antibody response

Abstract
Background: Hemodialysis patients are at high risk for severe COVID-19 disease. Despite a high early seropositivity rate, dialysis patients mount a dampened immune response following two doses of an mRNA vaccine. This study aimed to evaluate the serologic response to a booster dose of BNT162b2 vaccine, 6 months after the second dose, among hemodialysis patients. ***Methods:*** This prospective study included 80 hemodialysis patients and 56 healthcare workers serving as controls. Serologic samples were evaluated before and ~3 weeks after the third vaccine dose. The primary outcomes were the seropositivity rate and the log-transformed anti-SARS-COV-2 S1 (RBD) IgG as a continuous variable after the third dose. Secondary outcomes were the proportion of participants with "high response," defined as antibody levels >1,000 AU/mL, and "robust response," defined as antibody levels >4,160 AU/mL, according to prespecified cutoff values associated with neutralizing antibodies. Univariate and multivariate analyses were conducted to identify predictors of antibody response. ***Results:*** Among 80 hemodialysis patients, seropositivity rates improved from 78% (62/80) before the third dose, up to 96% (77/80) after the booster dose. The S1-RBD log-transformed antibody level increased significantly following the third dose from 2.15 ± 0.75 to 3.99 ± 0.83 compared with 2.65 ± 0.4 to 4.31 ± 0.42 in the control group. Among the hemodialysis patients, 88% (70/80) became "high responders" (>1,000 AU/mL), and of these, 79% (63/80) mounted a "robust response" (>4,160 AU/mL). Baseline antibody level, dialysis therapy, and hypoalbuminemia were independent predictors of impaired antibody response. ***Conclusions:*** A third dose of BNT162b2 COVID-19 vaccine, 6 months after the standard two-dose vaccination regimen, substantially improved humoral response in hemodialysis patients.

Introduction

Hemodialysis patients (HDP) are at high risk for severe COVID-19, with a case fatality rate above 20% [1]. Most incenter hemodialysis units cannot adequately maintain strict isolation procedures, and this coupled with an impaired immune response and high prevalence

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of comorbidities makes HDP a particularly susceptible population to COVID-19 infection [2]. Despite innovative therapeutics and vaccines, the COVID-19 pandemic remains a worldwide problem and is evolving constantly with recurrent surges. Hence, it is essential to try and establish an efficient vaccination strategy with sustainable protection against SARS-COV-2, especially in vulnerable populations such as HDP [3].

Vaccine efficacy is known to decline with decreasing kidney function. For example, HDP have a dampened immune response and weaker maintenance of protective antibodies in response to the common hepatitis B virus vaccine, and this led to changes in the internationally accepted hepatitis B immunization schedule for HDP [4]. In line with the above, the protection level achieved by HDP, in response to the standard anti mRNA-COVID-19 vaccine regimen of two doses, is impaired. Although a high seroconversion rate following two doses of the anti mRNA-COVID-19 vaccination has been seen in HDP, the antibody response was delayed, and the seroconversion rate and antibodies titers were substantially lower when compared with age-matched controls [5–9]. Several studies that assessed vaccine-induced neutralizing antibodies against SARS-COV-2 in HDP found a late induction and a decreased final neutralizing antibody capacity [3, 7, 10]. Furthermore, Espi et al. [3] recently showed that although vaccination reduced the number of COVID-19 infection events, the incidence of overt infection among two-dose vaccinated HDP is higher than what has been reported in the general population. And moreover, despite an increased proportion of mild and moderate forms of COVID-19 in vaccinated patients, more than 10% of HDP that received two doses of the mRNA vaccine subsequently died from COVID-19 infection [3]. Therefore, the known evidence of impaired immune response among HDP coupled with the high mortality rates from COVID-19 infection supports the need to study an intensification of the standard two-dose scheme with BNT162b2 vaccine in these patients.

In July 2021, the administration of a third (booster) dose of BNT162b2 vaccine was approved in Israel for very high-risk population such as severely immunocompromized and solid organ transplant recipients. One month later, the third dose was offered to the whole population, at least 5 months after the second dose [11].

In this current study, we aimed to evaluate humoral response among HDP after a late third dose of the BNT162b2 vaccine dose, given to patients at least 6 months following the second vaccine dose. We also tried to identify predictors of a positive antibody response.

Materials and Methods

This is a prospective comparative study conducted in continuation with our previous study, evaluating humoral response following a two-dose schedule of BNT162b2 vaccine among dialysis patients [12]. In the current HDP cohort, we included hemodialysis adult patients (age >18 years) who received all vaccine doses after chronic dialysis treatment initiation and participated in the previous study. The 80 HDP who were included in the current final cohort were compared with 56 healthcare workers (HCW) controls. Patients who had documented infection with COVID-19 at any time were excluded from the study. All the participants received a third BNT162b2 vaccine dose (V3) from Pfizer-BioNTech of 30 μg (0.3 mL) according to the Pfizer and the Israeli Ministry of Health recommendation for the entire adult population, at least 6 months after the second dose (V2).

Patients and control groups were followed for 8 weeks following vaccine administration, for breakthrough SARS-CoV-2 infection events. Clinical, demographic, and laboratory data were obtained by questioning and electronic medical records of both HDP and control groups. Blood samples for anti-SARS-COV-2 IgG levels were taken during the routine hemodialysis treatments, approximately 3 weeks before and 3 weeks after V3. Blood samples for anti-SARS-COV-2 IgG were collected before the commencement of a hemodialysis session. Blood samples from the control group were collected in the outpatient clinic during the same time period, approximately 3 weeks before and 3 weeks after V3, SARS-CoV-2 IgG II Quant (Abbott©) assay was used for quantitative measurement of IgG antibodies against the receptor-binding domain of the spike protein (anti-S1-RBD IgG). The cutoff for positivity is 50 arbitrary units per ml (AU/mL). An anti-S1-RBD IgG concentration of 1,050 AU/mL, 3,550 AU/mL, 4,160 AU/mL, and 6,950 AU/mL corresponds to a 95% probability of being at or above a plaque reduction neutralization test with 50% inhibition of infection of cultured cells (PRNT50) dilution of 1:80, 1:160, 1:250, and 1:640, respectively [13]. On the basis of the results of the World Health Organization International Standard study [14], the mathematical relationship of the Abbott unit (AU/mL) to the World Health Organization binding antibody units follows the equation: binding antibody units/mL = 0.142× AU/mL [13].

The primary outcomes were the seropositivity rate and the log-transformed anti-S1-RBD antibodies as a continuous variable following the third vaccine dose. Secondary outcomes were the proportion of "high response" above >1,000 AU/mL and "robust response" >4,160 AU/mL.

Statistical Analyses

Categorical variables are presented as numbers (percentages) and continuous variables as median (interquartile range, IQR) or mean (SD), according to their distribution. The former is compared using the χ^2 test or Fisher's exact test and the latter using *t* test or Mann Whitney U test, as appropriate.

Univariate and multivariate logistic regression models were used for evaluation of predictors for response. All variables were introduced into multivariate analysis after testing for collinearity, using forward regression model with *p* value below 0.05 used for inclusion. Linear regression analyses were performed to explore factors associated with higher log-transformed antibody titer among HDP.

General linear model was used for comparison of the log-transformed antibodies level between the HDP and HCW groups. Age, gender, body mass index (BMI), and diabetes status were introduced into the fixed-effect model as covariates. Estimated marginal mean adjusted to the above variables was calculated to evaluate the adjusted difference of the log antibodies level with 95% confidence interval (95% CI). Analyses were performed using IBM SPSS statistics, version 27.

Results

Participants' Characteristics

Of the 122 HDP in the original cohort (12), 80 (66%) had a baseline anti-S1-RBD-IgG test collected before the third vaccine dose (V3) and together with 56 HCW controls were included in this current study (Fig. 1). The mean age in the HDP group was 72.6 years (SD 11.7), as compared to 69.3 years (SD 5.32) in the HCW group. Diabetes mellitus (58.8%, 47/80) and male sex (70%, 56/80) were more common among HDP than HCW (12.5%, 7/56; 52%, 29/56, respectively). BMI was comparable between the groups (26.92 ± 4.98 vs. 26.63 ± 3.43) (Table 1). Six HDP, under chronic immunosuppression treatment, were included in the current study (Fig. 1).

Seropositivity Rate and S1-RBD Antibody Response to a Third Dose of BNT162b2 Vaccine

The seropositivity rate (>50 AU/mL) in the HDP group substantially improved after V3 from 77.5% (62/80) to 96.3% (77/80). Only three HDP (3/80) remained seronegative following V3. The anti-S1-RBD-IgG titer increased significantly following V3 from a median level of 153 [IQR 56–409] AU/mL to 15,529 [IQR 5,634–39,314] AU/mL. The log-transformed antibody level increased from 2.15 ± 0.75 log AU/mL to 3.99 ± 0.82 log AU/mL, while the age-adjusted log-transformed antibody level increased from 2.16 (95% CI 2.01–2.36) to 4.01 (95% CI 3.85–4.16).

In the HCW group, the baseline seropositive rate before V3 was high: 98.2% (55/56). The only patient who was seronegative seroconverted following V3. The baseline anti-S1-RBD-IgG level in the HCW group was significantly higher than in the HDP group (median 514 [IQR 259–857] AU/mL) ($p < 0.001$). After V3, a substantial increase in the antibody titer to 23,800 [IQR 13,343–41,511] AU/mL was documented. The log-transformed antibody level increased from 2.65 ± 0.4 log AU/mL to 4.31 ± 0.41 log AU/mL, and the age-adjusted log-transformed antibody increased from 2.63 (95% CI 2.43–2.83) to 4.29 (95% CI 4.1–4.48).

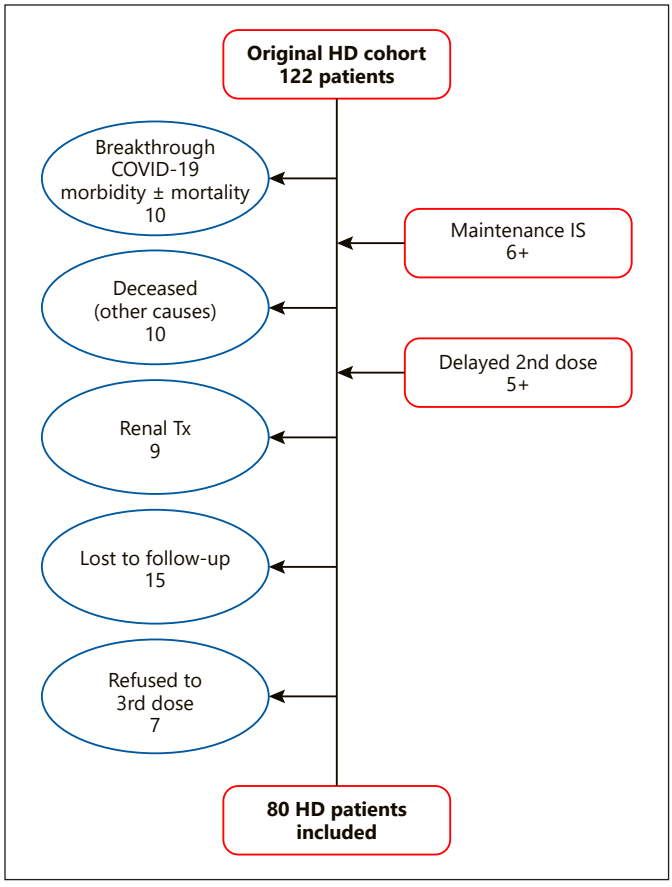

Fig. 1. Flowchart of the study.

Despite a substantial improvement in the anti-S1-RBD-IgG level in both HDP and HCW, the mean difference between the two groups decreased following V3 (mean difference 0.5, [95% CI 0.3–0.7] vs. 0.3 [95% CI 0.1–0.5], before and after V3, respectively, $p = 0.045$). Among the 6 HDP patients under chronic immunosuppression, only 3 (50%) patients were seropositive pre-V3. Following the third dose, 1 patient became seropositive, while the 2 other patients remained seronegative. The median anti-S1-RBD-IgG titer among the HDP under chronic immunosuppression treatment before V3 was 84.56 AU/mL (range: 0 to 724 AU/mL) and increased to 10,686 AU/mL (range: 1.6 to 18,360 AU/mL) post-V3.

Using two reported prespecified cutoff values, >1,000 AU/mL and >4,160 AU/mL, which were previously shown to be correlated with neutralizing antibodies (3, 13, 15–17), a vigorous response was seen following V3. Before V3, only 7.5% (6/80) in the HDP group and 17.9% (10/56) in the HCW group had a "high" anti-S1-RBD-IgG level above 1,000 AU/mL. After the third dose, in the

Table 1. Baseline characteristic and antibody response to a third dose of BNT162b2 vaccine in HD patients compared with controls

	All participants (136)	HDP (80)	HCW (56)	*p* value
Age (year) ±SD	71.25±9.77	72.61±11.78	69.3±5.32	0.052
Female (%)	51 (37.5%)	24 (30%)	27 (48.2%)	<0.001
Diabetes mellitus (%)	54 (39.7%)	47 (58.8%)	7 (12.5%)	<0.001
BMI (per kg/m^2) ±SD	26.8±4.42	26.92±4.98	26.63±3.43	0.712
Baseline Ab level before V3 (AU/mL, median [IQR])	310 [95–694]	153 [56–409]	514 [259–857]	<0.001
Baseline log Ab level (log AU/mL, mean ± SD)	2.35±0.68	2.15±0.75	2.65±0.4	<0.001
Baseline age-adjusted log Ab level (95% CI)	-	2.16 (2.01–2.36)	2.63 (2.43–2.83)	0.001
Baseline seropositive – Ab>50 AU/mL	117 (86%)	62 (77.5%)	55 (98.2%)	<0.001
Baseline high responders – Ab >1,000 AU/mL	16 (11.8%)	6 (7.5%)	10 (17.9%)	0.102
Baseline robust responders – Ab >4,160 AU/mL	2 (1.5%)	2 (2.5%)	0.00	0.512
Ab level after V3 (AU/mL, median [IQR])	18,245 (9,091–39,592)	15,529 (5,634–39,314)	23,800 (13,343–41,511)	0.037
Log Ab level±SD (log AU/mL, mean ± SD)	4.12±0.7	3.99±0.83	4.31±0.42	0.009
Age-adjusted log Ab level (95% CI)	–	4.01 (3.85–4.16)	4.29 (4.1–4.48)	0.024
Seropositive – Ab >50 AU/mL	133 (97.8%)	77 (96.3%)	56 (100%)	0.143
High responders – Ab >1,000 AU/mL	124 (91.1%)	70 (87.5%)	54 (96.4%)	0.071
Robust responders – Ab >4,160 AU/mL	115 (84.6%)	63 (78.8%)	52 (92.9%)	0.025

Baseline characteristic and antibody response to a third dose of BNT162b2 vaccine in HDP compared with healthy controls. Antibody response – anti-SI-RBD IgG levels in AU/mL. V3, third dose of BNT162b2 vaccine; HDP, hemodialysis patients; HCW, healthcare workers.

HDP group, 87.5% (70/80) became "high responders" (>1,000 AU/mL) while 78.8% (63/80) mounted a "robust response" (>4,160 AU/mL). In the HCW group, 96.4% (54/56) became "high responders" (>1,000 AU/mL) and 92.9% (52/56) became "robust responders" (>4,160 AU) (Table 1; Fig. 2).

Predictors of S1-RBD Antibody Response to the Third Dose of BNT162b2 Vaccine in HDP

To evaluate general predictors of antibody response among all study participants (HDP and HCW), we used linear regression analysis and evaluated the log-transformed antibody level as a continuous variable by univariate analysis. The only factors that were significantly associated with the log-transformed antibody level after V3 were the need for dialysis therapy (B; −0.16, 95% CI −0.04 to −0.28, $p = 0.009$) and baseline antibody level before V3 (B; 0.75, 95% CI 0.63–0.87, $p < 0.001$). We did not find any significant relation between age, gender, BMI or diabetes status, and antibody response (online suppl. Table S1; see www.karger.com/doi/10.1159/000525519 for all online suppl. material).

Univariate and multivariate analysis for specific predictors among the HDP group alone demonstrated that the variables associated with the log-transformed antibody level after V3 included hypoalbuminemia (B; −0.5, 95% CI −0.95 to −0.05, $p = 0.03$) and log-transformed antibody level pre-V3 (B; 0.71, 95% CI 0.53–0.89, $p < 0.001$). Chronic immunosuppression was associated with poor response to V3, in the univariate analysis only (B; −1.01 per year, 95% CI −1.63 to −0.4, $p = 0.002$). However, this association was not significant in the multivariate analysis (B; −0.38 per year, 95% CI −0.84 to 0.08, $p = 0.105$) (Table 2). Notably, antibody response following V3 in the HDP group was well correlated not only with the baseline antibody level before V3 (6 months following V2) but also with the antibody level at 1 month following V2 (Pearson correlation 0.718, $p < 0.001$ and 0.828, $p < 0.001$, respectively).

Tolerance and Outcome

Overall tolerance to the third dose of BNT162b2 mRNA vaccine was excellent among all the study participants in both groups. No participant developed severe side effects requiring hospitalization. Only three cases of COVID-19 infection among HDP and no case among the HCW group were diagnosed during a follow-up period of up to 8 weeks following V3. Two cases were mild with favorable outcomes. The third case was defined as mod-severe, with complete recovery.

Discussion

In this study including 80 dialysis patients, an excellent antibody response to the third dose of BNT162b2 vaccine was found. We documented a high seropositivity rate of

Table 2. Multivariate analysis for predictors of S1-RBD antibody levels in response to a third dose of BNT162b2 in HD patients

Variable	HD patients, $N = 80$	Univariate		Multivariate	
		B (95% CI)	*p* value	B (95% CI)	*p* value
Age (per year)	72.61±11.8	−0.01 (−0.03 to 0.0)	0.156	–	–
Female sex	24 (30%)	0.11 (−0.29 to 0.52)	0.574	–	–
Dialysis vintage (per month)	41.27±34	−0.003 (0.002–0.008)	0.470	–	–
Diabetes mellitus	47 (59%)	−0.03 (−0.41 to 0.35)	0.876	–	–
IHD	40 (50%)	−0.053 (−0.42 to 0.32)	0.777	–	–
Malignancy Hx	19 (24%)	−0.23 (−0.67 to 0.2)	0.281	–	–
Chronic IS	7 (9%)	−1.01 (−1.63 to −0.4)	0.002	−0.38 (−0.84 to 0.08)	0.105
Dialysis access (catheter)	34 (43%)	0.12 (−0.25 to 0.5)	0.512	–	–
KT/V	1.44±0.26	0.069 (−0.64 to 0.78)	0.848	–	–
nPCR	1.14±0.29	0.11 (−0.35 to 0.57)	0.630	–	–
Residual renal function	36 (45%)	−0.07 (−0.44 to 0.31)	0.724	–	–
BMI (per kg/m^2)	26.9±5	0.02 (−0.02 to 0.06)	0.271	–	–
Log Ab before V3	2.15±0.75	0.8 (0.63–0.97)	<0.001	0.71 (0.53–0.89)	<0.001
Hemoglobin (per g/dL)	10.68±1.18	−0.02 (−0.17 to 0.14)	0.842	–	–
Albumin <3.5 g/dL)	7 (9%)	−0.95 (−1.57 to −0.33)	0.003	−0.5 (−0.95 to −0.05)	0.030

Multivariate analysis for predictors of S1-IgG antibody levels in response to a third dose of BNT162b2 vaccine in HDP. Multivariate analysis of factors associated with the serologic response (log-transformed anti-SI-RBD IgG levels in AU/mL) in HDP vaccinated with a third dose (V3) of BNT162b2 vaccine. B >0 indicates a positive correlation with the log antibody titer. For linear regression, all variables with $p < 0.05$ in univariate association were inserted. IHD, ischemic heart disease; IS, immunosuppression; BMI, body mass index; *n*PCR, normalized protein catabolic rate; ESA, erythropoietin stimulating agents.

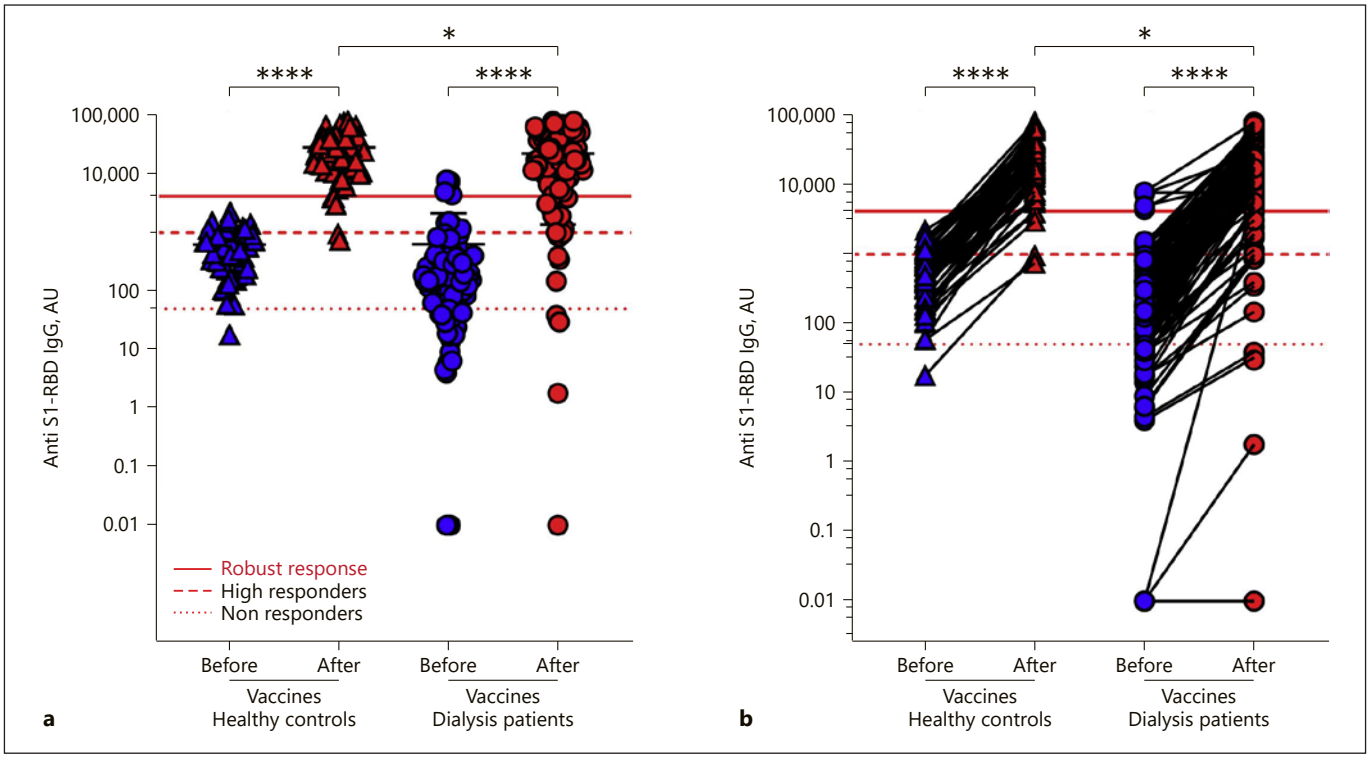

Fig. 2. Antibody response before and after a third dose of BNT162b2 vaccine. The anti-S1-RBD IgG level before and after a third vaccine dose in HDP and healthy control. Results refer to the HDP group ($n = 80$) and HCW group ($n = 56$).

96%, which increased from 77.5% before V3. The S1-RBD antibody level following V3 increased significantly in HDP and age-matched control groups, while the mean difference between the two groups decreased. Furthermore, according to prespecified cutoff values which were previously reported to be associated with neutralizing capacity of the serum, 87.5% (70/80) in the HDP group became "high responders" (anti-S1-RBD-IgG >1,000 AU/mL), and 78.8% (63/80) became "robust responders" (anti-S1-RBD-IgG >4,160 AU/mL). Baseline antibody level, the need for dialysis therapy, and hypoalbuminemia were independent predictors of inferior antibody response to a late third dose of BNT162b2 vaccine.

A large 6-month prospective study involving vaccinated HCW demonstrated a significant waning of anti-spike IgG and neutralizing antibodies over a 6-month period following two doses of BNT162b2 vaccine [15]. Our study has also documented decreased anti-S1-RBD-IgG titer 6 months following the standard two-dose vaccine regimen in both groups of HCW and HDP. However, the pre-V3 median antibody titer of the HDP group was substantially lower as compared with the median antibody titer in the HCW group.

In an aim to extend the protection achieved by the vaccine among high-risk populations, intensification of vaccine schedule has been suggested. Several studies that evaluated the efficacy of an early third dose (1–2 months after the second dose) among HDP reported an increase in the antibody level [16, 17]. Notably, the elevation in the antibody response following V3 was more substantial in patients with low antibody levels after the second dose [3, 18, 19] and with a longer interval between V2 and V3 [19].

Nevertheless, Payne et al. found that SARS-COV-2-neutralizing antibody titers were higher after an extended dosing interval (6–14 weeks), compared to the conventional 3–4-week regimens for the second vaccine dose of BNT162b2 [20]. This finding rationalizes extending the interval between the second and third doses to maximize booster benefit. Indeed, despite the considerable waning of anti-S1-RBD-IgG 6 months following V2, this study documented a vigorous response with high median antibody titers following V3. Although yet to be established, a high correlation between the increased level of anti-S1-RBD-IgG and neutralizing capacity of the serum has been demonstrated [21]. Using two different incremental prespecified cutoff values, previously shown to correlate with virus neutralization [3, 13, 22–24], this study found that 80% of HDP became "high responders" (>1,000 AU/mL), while 76% became "robust responders" (>4,160 AU/mL) following the late third dose. Furthermore, in contrast to the efficacy of the early third dose that seems to be limited to specific HDP subgroups, we documented favorable results in the entire HDP cohort, while the best predictor of antibody response was an elevated baseline antibody titer. Either antibody response 1 month or 6 months following V2 was highly positively correlated to antibody response following the late booster. Therefore, to take full advantage of the booster, our findings support postponing the third dose and providing it after antibody waning and protection diminution to all HDP, without the need for unnecessary screening tests.

The need for dialysis treatment and hypoalbuminemia (serum albumin <3.5 g/dL) were independent predictors associated with inferior antibody response following V3 in HDP. The uremic state and hypoalbuminemia are established as being associated not only with poor nutritional status but also with hypercatabolic state and chronic inflammation. Both poor nutritional status and chronic inflammatory state can negatively influence adequate humoral and cellular immunity. Accumulation of uremic toxins and chronic inflammation might contribute to impaired humoral response in the uremic state. Nonetheless, the malnutrition inflammation complex syndrome may also cause, impaired immunity and high mortality among dialysis patients [2, 4, 25]. This finding is consistent with our first report about the association between hypoalbuminemia below 3.5 g/dL and inferior antibody response to two doses of BNT162b2 among HDP [12]. In agreement, several other studies identified hypoalbuminemia in HDP as a major predictor of impaired response to the COVID-19 vaccine that may be modified before the vaccination protocol [23, 26, 27].

Chronic immunosuppression was associated with a reduced response to V3 in the univariate analysis but not in the multivariate analysis. These unequivocal results are probably due to the small size of the particular group that was analyzed in this study. Immunosuppression is a well-known predictor for weak immunogenicity of mRNA vaccine, in either solid organ transplant recipients or immune-mediated inflammatory diseases [23, 28]. A strategy of transient diminution of the immunosuppressive protocol prior to and shortly after the vaccine has been suggested [29].

Both age and diabetes are considered risk factors for poor response to vaccination. However, these correlations were inconsistent in previous studies [9]. Although in our previous report, age was found to be an independent predictor of antibody response post-V2, in this study, no inverse linear association was detected between age or diabetes and immunogenicity rates following V3

[12]. Intriguingly, Van Praet et al. [23] reported that increased age was an independent predictor of the early immune response but not for the long-term immune response to SARS-CoV-2 mRNA vaccine.

Patient tolerance to the third vaccine dose was excellent, without any major adverse reactions. Only three cases of COVID-19 infection among HDP and no case among HCW group were diagnosed during a follow-up period of up to 8 weeks following V3. Two cases were defined as mild or asymptomatic with favorable outcomes. The third patient had a mod-severe disease, with complete recovery following treatment. Of note, this patient got ill before the antibodies sampling post-V3 was taken, and the case was not included in this study. However, this patient was negative for S1-RBD antibodies post-V2 as well as pre-V3.

This study has several limitations. It was conducted as a single-center study with a small-sized group, which limited statistical analyses and could induce bias. We assessed for anti-S1-RBD-IgG response only. We did not assess for anti-N antibodies to recognize undocumented infections. However, routine PCR surveys have been frequently conducted in our dialysis units during the study period. Therefore, most of the infections including the asymptomatic events were documented. Furthermore, neither cellular response nor neutralizing antibodies were directly assessed. Although the neutralizing antibodies level is a more precise predictor of immune protection, their assessment is not practical in clinical practice. Therefore, we used two incremental prespecified cutoff values of 1,000 AU/mL and 4,160 AU/mL of S1-RBD antibodies as a surrogate, as previously described. Both Espi et al. [3] and Robert et al. [16] found a substantial increase of neutralizing antibodies following the third dose with a high correlation to the S1-RBD-IgG response among HDP. Nevertheless, the third dose of vaccine did not result in a significant increase in the cellular response [3].

In summary, given the increased risk for severe COVID-19 disease, together with the impaired immunogenicity of the vaccine in these high-risk patients, there is an urgent need to extend the duration of vaccine efficacy among patients on hemodialysis. A late third dose of BNT162b2, 6 months after the second vaccine dose, improved S1-RBD antibody response over two doses in HDP. Despite a significant antibody waning, the seropositivity rate in the HDP group substantially increased, and the antibody titers robustly boosted close to the control group. These findings strongly support the importance of standard vaccine regimen intensification with repetitive booster doses in HDP.

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Statement of Ethics

This study protocol was reviewed and approved by the local Ethics Committee of the Rabin Medical Center, Israel, approval number 0096-21-RMC. A written informed consent was obtained from all participants to participate in the study.

Conflict of Interest Statement

The authors of this manuscript have no conflicts of interest to disclose. The results presented in this article have not been published previously in whole or part.

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Author Contributions

All of the authors contributed significantly to this work and approve this manuscript submission. Timna Agur, Michal Herman-Edelstein, Benaya Rozen-Zvi, and Boris Zingerman – research design, data collection and analysis, and writing the paper. Naomi Ben-Dor, Weaam Alkeesh, Tali Steinmetz, and Ruth Rachamimov – data collection and analysis. Asher Korzets – critical review of the paper.

Data Availability Statement

The original data from this study may be available upon reasonable request to the corresponding author.

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