

## Assessment of Antibody Titers after 6 Months of Vaccination against SARS-COV-2 in Patients with CKD Stage 4, 5 and CKD 5d

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### Abstract

**Background:** Since the pandemic of COVID-19 started from December 2019, remarkable numbers of infections and deaths associated with COVID-19 have been recorded worldwide. Chronic kidney disease patients are particularly at high risk of infections due to impairments in the innate and adaptive immune systems. Adequate humoral (antibody) and cellular (T cell-driven) immunity are required to minimize pathogen entry and promote pathogen clearance to enable infection control. Vaccination can generate cellular and humoral immunity against this specific pathogen. COVID-19 prevention through successful vaccination is therefore paramount in chronic kidney disease population. But vaccination efficacy is diminished in these patients because premature ageing of the immune system and chronic systemic low- grade inflammation are the main causes of immune alteration in these patients. Therefore, it is urgently necessary to establish a different vaccination strategy for chronic kidney disease and dialysis patient in terms of the dose and administration time.

**Aims:** This study aimed to assessment of antibody titers after vaccination against SARS-COV-2 in patients with chronic kidney disease stage 4, 5 on conservative management and maintenance haemodialysis. **Methods:** This prospective observational comparative was conducted in Nephrology department of Dhaka Medical College Hospital. Selection of patients was done by purposive sampling according to inclusion and exclusion criteria. Total 135 patients distributed in three groups: 45 patients of chronic kidney disease (CKD) stage 4, 5 on conservative management, 45 patients on maintenance haemodialysis (MHD) and 45 healthy controls were approached for the study who were receiving SARS-COV-2 vaccination. Demographic, clinical and laboratory data were collected initially. At first a pre vaccination sample or 1<sup>st</sup> sample was taken for antibody measurement. Then participants from all groups were given 2 doses MODERNA vaccine containing 100 µg in 0.5 ml each in 28 days apart. Then after 14 days of 1<sup>st</sup> dose of vaccination the 2<sup>nd</sup> samples were taken, 3<sup>rd</sup> samples were taken 14 days after the 2<sup>nd</sup> dose vaccination. Study populations were subdivided into two groups according to pre vaccination SARS-COV-2 antibody titer; seropositive- positive response before vaccination and seronegative- negative response before vaccination. They were also divided into two groups according to quantitative antibody response; positive response- values  $\geq 10$  DU/mL were positive Negative response- values of  $<10$  DU/mL were negative. **Result:** Seroconversion rate was around 20% among study participants before vaccination. 14 days after the 1<sup>st</sup> dose of vaccination, 90.04% patients had positive immune response in CKD stage 4, 5 on conservative management group whereas in MHD group 84.82% responded to vaccination and immune response in control group was 100%. Immune response is 100% among all the groups after 14 days of 2<sup>nd</sup> dose of vaccination but the concentration of antibody differs significantly among the study groups. Responders were comparatively younger with normal BMI. **Conclusion:** Haemodialysis patients as well as patients with chronic kidney disease stage 4, 5 on conservative management showed a favorable but profoundly lower early antibody response, which decreased substantially during follow-up.

**Keywords:** Covid-19, Corona virus, CKD, MHD.

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## INTRODUCTION

Corona viruses were described for the first time in 1966 by Tyrell and Bynoe, who cultivated the viruses from patients with common colds. They are enveloped, positive, single-stranded large RNA viruses that not only infect humans, but also a wide range of animals (bats, pangolins, cats, pigs and birds, among others) (Tyrell *et al.*, 1966). Corona virus disease 2019 (COVID-19) is defined as illness caused by a novel corona virus called severe acute respiratory syndrome corona virus 2 (SARS-CoV-2; formerly called 2019-nCoV), which was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China (Centers for Disease Control and Prevention, 2020).

The clinical spectrum of COVID-19 infection is very variable, ranging from asymptomatic infection, anosmia, ageusia or minor upper respiratory tract illness to severe pneumonia with respiratory failure and even death (Zhou *et al.*, 2020). Diarrhoea and cutaneous and thrombotic manifestations were also described. More severe cases with higher rates of mortality have been reported in older patients and in those with chronic illness such as cardiovascular disease, hypertension, diabetes and kidney failure patient (Tang *et al.*, 2020).

Chronic kidney disease (CKD) constitutes a serious global health problem. According to the Global Burden of Disease study, incidence of CKD reached 9.1% in 2017, resulting in 697.5 million cases worldwide (Bikbov *et al.*, 2020). A marked increase in the mortality rate associated with CKD was also noted, which accounted for 4.6% of global deaths and thereby placed CKD as 12th leading cause of death globally in 2017 (Cockwell and Fisher, 2020). Progressive declines in renal function eventually result in end-stage kidney disease (ESKD), with 2.5 million patients who require renal replacement therapies, such as kidney transplantation or dialysis, and this number is expected to double by 2030 with huge sanitary costs (Liyanage *et al.*, 2015). Renal failure and dialysis treatment are associated with disorders of the innate and adaptive immunosystem, contributing to the increase of infection rate (Kato *et al.*, 2008). Indeed, infectious disease is the second most common cause of death after cardiovascular disease in patients with CKD (Reddy, Chitturi and Yee, 2019).

COVID-19 pandemic has disproportionately affected patients with chronic kidney disease and on dialysis. Although SARS-CoV-2 sero prevalence among patients on dialysis is similar to the general population (Bajema *et al.*, 2021). Immune dysregulation caused by uremia is characterized not only by immune depression that makes this patient group prone to acquiring COVID-19 during their hospital visits, but also immune activation that predisposes to cardiovascular diseases, placing an additional risk for severe COVID-19 disease (Yen *et al.*, 2021).

A 20-30-fold higher mortality rate compared with the general population seen in patient with CKD. More recent data continue to show mortality rates in this population in excess of 15% (Hsu *et al.*, 2021). Hospitalization rates have been 3-to-4 fold higher than other Medicare beneficiaries (Centers for Medicare & Medicaid Services, 2020). Nearly one-third of patients receiving dialysis died after hospitalization with COVID-19 (Ng *et al.*, 2020).

Control measures such as the use of masks, physical distancing, testing of exposed or symptomatic persons, contact tracing and isolation have helped limit the transmission where they have been rigorously applied; however, these actions have been variably implemented and have proved insufficient in impeding the spread of coronavirus disease 2019 (Covid-19). Vaccines are needed to reduce the morbidity and mortality associated with Covid-19 and multiple platforms have been involved in the rapid development of vaccine candidates (Ramasamy *et al.*, 2020). Several vaccines have been approved for SARS-CoV-2 infection. Live attenuated vaccines generally should be avoided in patients on maintenance HD due to their dysregulated immune system. Both the mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) and the replication-defective viral-vectored vaccines, such as ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and an inactivated virus COVID-19 vaccines (Sinopharm COVID-19 vaccine) are considered safe for use in patients treated with maintenance HD (Windpessl *et al.*, 2021). The mRNA vaccine platform has advantages as a pandemic-response strategy, given its flexibility and efficiency in immunogenic design and manufacturing. Earlier work had suggested that the spike protein of the coronavirus responsible for the 2002 SARS outbreak was a suitable target for protective immunity (He *et al.*, 2006).

Our study result indicated that the placebo group had 14,164 participants with 769 SARS-CoV-2 infection cases, while the mRNA-1273 group comprised 14,287 subjects with 56 COVID-19 incidents. The vaccine efficacy rose steadily to a peak of 94.1% on day 120, successive to 92.6% 40 days following the initial dose. At around 120 days, the vaccine efficacy began to decline, and it had fallen to 89.6% by 200 days (Pouwels *et al.*, 2021).

In this regard, patients on dialysis for vaccination have been at the forefront of SARS-CoV-2 vaccination programs internationally. Response to vaccination can be considerably lower in patients with severely impaired kidney function due to the immunosuppressive effect of uremia and specific medications. This has been shown for vaccination against hepatitis B, influenza, and Streptococcus pneumonia (Sanders., 2022). Chronic kidney disease impairs both natural and adaptive immune response, which might be the culprit for the lower seroconversion

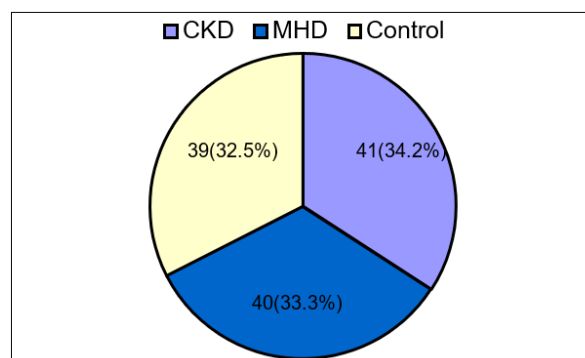
rates seen in dialysis patients (Alcázar-Arroyo *et al.*, 2021).

## MATERIAL & METHODS

This Prospective observational comparative study was conducted in the Department of Nephrology, Dhaka Medical College and Hospital, Bangladesh from January 2021 to July 2022. After informed written consent from parents/guardians, a total number of 120 Chronic kidney disease stage 4, 5 on conservative management and maintenance hemodialysis (MHD) patients who were receiving SARS- COV-2 vaccine were included in the study. Individuals with COVID- 19 related clinical signs, e.g., fever, coughing, runny nose, sore throat, dyspnea, shortness of breath, aches and pain at the time of sample collection, malignancy, history of organ transplantation, taking immunosuppressive medications (including cytotoxic agents and systemic corticosteroids), HIV/AIDS infection, Pregnancy and Age <18 years were not considered for enrollment in the study. Detailed history and all clinical examination were done focusing on age, gender, medications, weight, height and body mass index (BMI). KDIGO 2012 clinical practice guideline for chronic kidney disease (CKD) was utilized for diagnosis and staging of CKD. CKD 4, 5 patients were withdrawn from the study if their renal function had deteriorated to the point that dialysis was needed. All Data was collected in a pre-tested questionnaire by taking history, examining the patients clinically, laboratory finding and patient outcomes. All data was recorded systematically in preformed data collection form. Data were analyzed by Statistical Package of Social Science (SPSS) version 26.

## RESULTS

This study was conducted in department of Nephrology, DMCH. After completion of two doses of SARS-COV-2 vaccination, antibody titer was measured before and 14 days after 1st dose of vaccination, then 14 days after 2nd dose of vaccination. The study subjects were divided into two groups according to pre vaccination antibody level- seropositive and seronegative. Different demographic, clinical and biochemical variables were compared among these groups. The results are presented by the following tables:



**Figure 1: Pie chart shows the CKD, MHD and control status of study patients (n=120)**

Pie chart shows the CKD, MHD and control status of study patients. It was observed that more than one third (34.2%) of patients were found CKD followed by 40 (33.3%) were MHD and 39 (32.5%) were control.

**Table I: Comparison of demographic profile with study groups (n=120)**

Demographic profile	CKD stage 4, 5 (n=41)		MHD (n=40)		Control (n=39)		p value
	n	%	n	%	n	%	
<b>Age (years)</b>							
≤50	23	56.1	22	55.0	30	76.9	
51-60	8	19.5	8	20.0	7	18.0	
>60	10	24.4	10	25.0	2	5.1	
Mean±SD	49.71±12.99		48.65±14.61		45.08±15.17		<sup>a</sup> 0.085 <sup>ns</sup>
Range (min-max)	27-76		24-78		23-63		
<b>Sex</b>							
Male	21	51.2	21	52.5	25	64.1	<sup>b</sup> 0.445 <sup>ns</sup>
Female	20	48.8	19	47.5	14	35.9	

ns= not significant

<sup>a</sup>p value reached from Kruskal Wallis test

<sup>b</sup>p value reached from Chi-square test

CKD= Chronic kidney disease MHD= Maintenance hemodialysis

Table I shows the comparison of demographic profile with study groups. It was observed that more than half (56.1%) of patients belonged to age was ≤50 years in CKD, 22 (55.0%) in MHD and 30 (76.9%) in control. The mean age was 49.71±12.99 years in CKD,

48.65±14.61 years in MHD and 40.08±11.17 years in control. More than half (51.2%) of patients were male in CKD, 21 (52.5%) in MHD and 25 (64.1%) in control. The differences of age were statistically significant (p<0.05) among three groups.

**Table II: Comparison of BMI with study groups (N=120)**

BMI (kg/m <sup>2</sup> )	CKD stage- 4, 5 (n=41)		MHD (n=40)		Control (n=39)		p value
	n	%	n	%	n	%	
Underweight	5	12.2	6	15.0	0	0.0	
Normal	19	46.3	16	40.0	29	74.4	
Overweight	12	29.3	15	37.5	6	15.3	
Obese	5	12.2	3	7.5	4	10.3	
Mean ± SD	23.0±3.2		22.1±2.1		24.3±3.7		<sup>a</sup> 0.007 <sup>s</sup>

s= significant ns= not significant

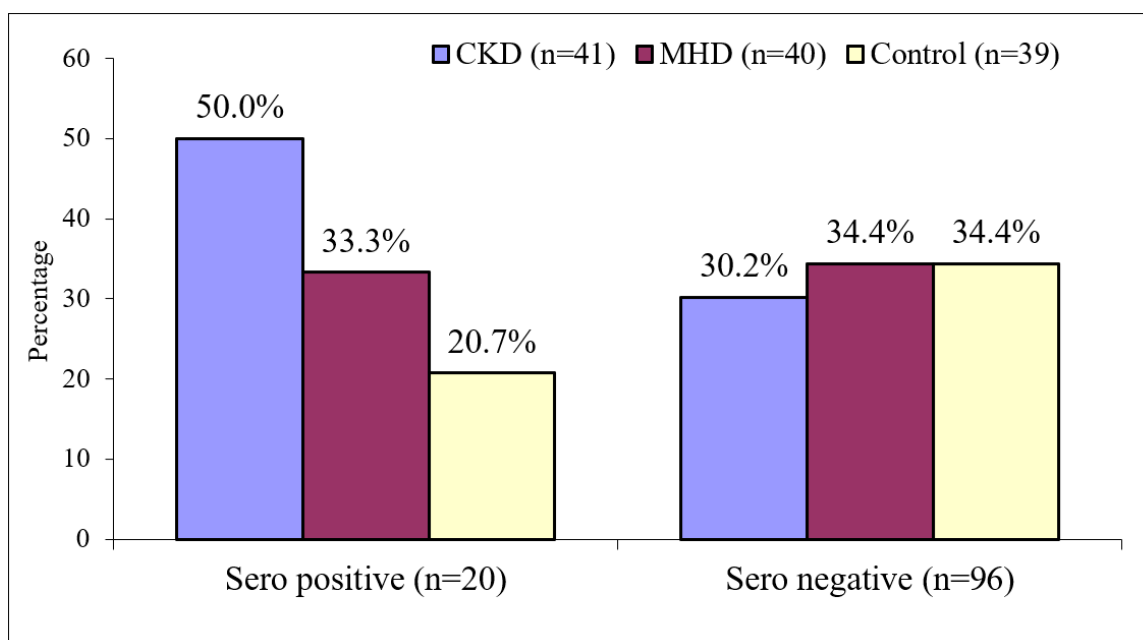
<sup>a</sup>p value reached from ANOVA test<sup>b</sup>p value reached from Chi-square test

BMI= Body mass index CKD= Chronic kidney disease

MHD= Maintenance hemodialysis

Table II shows the comparison of BMI with study groups. It was observed that almost half (46.3%) of patients belonged to BMI was normal in CKD, 16 (40.0%) in MHD and 29 (74.4%) in control. The mean

BMI was 23.0±3.2 kg/m<sup>2</sup> in CKD, 22.1±2.1 kg/m<sup>2</sup> in MHD and 24.3±3.7 kg/m<sup>2</sup> in control. The differences of BMI were statistically significant (p<0.05) among three groups.

**Figure 2: Bar diagram shows the Comparison of pre vaccination seroconversion with CKD, MHD & control patients (n=120)**

CKD= Chronic kidney disease MHD= Maintenance hemodialysis

Bar diagram shows the Comparison of pre vaccination seroconversion status with CKD, MHD & control groups. In seropositive, it was observed that half 11 (50.0%) of patients had CKD followed by 8 (33.3%)

had MHD and 5 (20.8%) were control. In seronegative, 29 (30.2%) patients had CKD, 33 (34.4%) had MHD and 34 (35.4%) were control.

**Table III: Comparison of antibody titers with pre vaccination seroconversion status (N=120)**

Anti-body level (DU/ml)	Seropositive (n=24)	Seronegative (n=96)	p value
	Mean± SD	Mean± SD	
2 <sup>nd</sup> sample (14 days after 1 <sup>st</sup> dose)	341.42±41.67	223.86±46.35	0.001 <sup>s</sup>
3 <sup>rd</sup> sample (14 days after 2 <sup>nd</sup> dose)	469.36±127.77	291.46±96.16	0.001 <sup>s</sup>

s= significant ns= not significant

p value reached from Unpaired-t test

Table III shows the comparison of pre vaccination seroconversion status with Anti-body titers. The mean 2<sup>nd</sup> sample was 341.42±41.67 in seropositive and 223.86±46.35 in seronegative. The mean 3<sup>rd</sup> sample

was 469.36±127.77 in seropositive and 291.46±96.16 in seronegative. The differences of 2<sup>nd</sup> sample and 3<sup>rd</sup> sample were statistically significant (p<0.05) with pre vaccination seroconversion status.

**Table IV: Comparison of antibody titers with study groups (N=120)**

Anti-body level (DU/ml)	CKD stage- 4, 5 (n=41)	MHD (n=40)	Control (n=39)	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
1 <sup>st</sup> sample (pre vaccination)	31.5±26.41	29.48±23.79	43.21±41.61	0.298 <sup>ns</sup>
2 <sup>nd</sup> sample (14 days after 1 <sup>st</sup> dose)	227.66±225.82	168.27±165.73	334.07±54.35	0.001 <sup>s</sup>
3 <sup>rd</sup> sample (14 days after 2 <sup>nd</sup> dose)	396.02±93.24	318.84±54.49	604.29±150.28	0.001 <sup>s</sup>

s= significant

ns= not significant

p value reached from ANOVA test

CKD= Chronic kidney disease MHD= Maintenance hemodialysis

Table IV shows the comparison of Anti-body titers with study groups. The mean 1<sup>st</sup> sample (pre vaccination) was 31.5±26.41 in CKD, 29.48±23.79 in MHD and 43.21±41.61 in control. The mean 2<sup>nd</sup> sample was 227.66±225.82 in CKD, 168.27±165.73 in MHD

and 334.07±54.35 in control. The mean 3<sup>rd</sup> sample was 396.02±93.24 in CKD, 318.84±54.49 in MHD and 604.29±150.28 in control. The differences of 2<sup>nd</sup> and 3<sup>rd</sup> sample mean were statistically significant (p<0.05) among three groups.

**Table V: Comparison of antibody titers with CKD stage 4, 5 on conservative management (N=120)**

Anti-body level (DU/ml)	CKD stage- 4 (n=20)	CKD stage- 5 (n=21)	p value
	Mean ± SD	Mean ± SD	
1 <sup>st</sup> sample (pre vaccination)	30.5±27.41	29.18±17.08	0.298 <sup>ns</sup>
2 <sup>nd</sup> sample (14 days after 1 <sup>st</sup> dose)	220.66±215.62	203.78±195.73	0.241 <sup>s</sup>
3 <sup>rd</sup> sample (14 days after 2 <sup>nd</sup> dose)	380.52±74.24	365.84±56.49	0.231 <sup>s</sup>

s= significant

ns= not significant

p value reached from ANOVA test

CKD= Chronic kidney disease

Table V shows the comparison of Anti-body titers with CKD- 4,5. The mean 1<sup>st</sup> sample (pre vaccination) was 30.5±27.41 in CKD and 29.18±17.08 in CKD-5. The mean 2<sup>nd</sup> sample was 220.66±215.62 in

CKD-4 and 203.78±195.73 in CKD-5. The mean 3<sup>rd</sup> sample was 380.52±74.24 in CKD-4 and 365.84±56.49 in CKD-5. The differences of 2<sup>nd</sup> and 3<sup>rd</sup> sample mean were not statistically significant (p<0.05).

**Table VI: Antibody titers after 14 days of completion of 1<sup>st</sup> dose of vaccination (2<sup>nd</sup> sample) in in study groups (N=120)**

Anti-body level (DU/ml)	CKD stage- 4, 5 (n=41)	MHD (n=40)	CONTROL (n=39)	p value
<b>Responder (108) (≥10 DU/ml)</b>	36 (90.04%)	33 (84.82%)	39(100%)	0.046 <sup>s</sup>
<b>Non-Responder (12) (&lt;10 DU/ml)</b>	5 (12.19%)	7 (21.21%)	0	
<b>Antibody titer (DU/ml) (Mean ± SD)</b>	227.66±225.82	168.27±165.73	334.07±54.35	0.001 <sup>s</sup>

s= significant p value reached from ANOVA test

CKD= Chronic kidney disease MHD= Maintenance hemodialysis

Table VI shows the antibody titers after 14 days of completion of 1<sup>st</sup> dose of vaccination. Among CKD stage 4-5 (ND) group 90.04% patients had immune response whereas in MHD group 84.82% responded to

vaccination and immune response in control group was 100%. Difference of immune response and antibody titer were significant among three groups (p < 0.05).

**Table VII: Antibody titers after 14 days of completion of 2nd dose of vaccination (3rd sample) in study groups (N=120)**

Anti-body level (DU/ml)	CKD stage- 4, 5 (n=41)	MHD (n=40)	CONTROL (n=39)	p value
<b>Responder (120) (<math>\geq 10</math> DU/ml)</b>	41 (100%)	40 (100%)	39 (100%)	---
<b>Non-Responder (0) (&lt;10 DU/ml)</b>	0	0	0	
<b>Antibody titer (DU/ml) (Mean <math>\pm</math> SD)</b>	396.02 $\pm$ 93.24	318.84 $\pm$ 54.49	604.29 $\pm$ 150.28	<sup>b</sup> 0.001 <sup>s</sup>

s= significant <sup>a</sup>p value reached from Chi-square test<sup>b</sup>p value reached from Kruskal Wallis test

Table VII shows the antibody titers after 14 days of completion of 2<sup>nd</sup> dose of vaccination. Immune response is 100% among all the groups after vaccination.

Difference of antibody titers were significant among study groups ( $p < 0.05$ ).

**Table VIII: Comparison of immune response according to age of study population (n=120)**

Age in years	1 <sup>st</sup> sample (pre vaccination)	2 <sup>nd</sup> sample (14 days after 1 <sup>st</sup> dose)	3 <sup>rd</sup> sample (14 days after 2 <sup>nd</sup> dose)	P value
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
$\leq 50$ years	30.65 $\pm$ 41.39	324.6 $\pm$ 47.48	441.36 $\pm$ 126.71	0.001 <sup>s</sup>
51–70 years	30.06 $\pm$ 44.7	322.63 $\pm$ 43.77	414.52 $\pm$ 121	0.001 <sup>s</sup>
> 70 years	15.42 $\pm$ 41.34	238.22 $\pm$ 44.18	295.53 $\pm$ 72.63	0.001 <sup>s</sup>

s= significant

P value reached from Kendall's W Test

Table VIII shows the association between age with anti-body titers. The ages level of  $\leq 50$  years, 51-70

years and > 70 years were statistically significant ( $p < 0.05$ ) with anti-body collection groups

**Table IX: Comparison of immune response in relation to BMI (N=120)**

Variables	Responder ( $\geq 10$ DU/ml)	Non-Responder (<10 DU/ml)	p value
<b>BMI (Kg/m<sup>2</sup>)</b>			
Underweight (11)	-	(30.3%)	
Normal (64)	(75.8%)	(44.8%)	
Overweight (33)	(24.2%)	(21.3%)	
Obese (12)	-	(3.6%)	
<b>Mean <math>\pm</math> SD</b>	23.1 $\pm$ 3.1	20.0 $\pm$ 3.2	<sup>a</sup> 0.018 <sup>s</sup>

s= significant ns= not significant <sup>a</sup>p value reached from Unpaired-t

Table IX shows the immune response to SARS-COV-2 vaccination in relation to BMI (Kg/m<sup>2</sup>). Three fourth (75.8%) of patients who had adequate response had normal range of BMI. Patients with extreme BMI (underweight & obese) did not achieve adequate response, there were more non responders. The differences of BMI were statistically significant ( $P < 0.05$ ) within different immune response groups.

## DISCUSSION

This study was carried out with an aim to observe the antibody response of SARS-COV-2 vaccines in healthy individuals and patients with chronic kidney disease stage 4, 5 on conservative management and on maintenance haemodialysis and measure the post vaccination antibody titers in those three groups. This was a prospective observational comparative study consisted of 45 patients with CKD stage 4, 5 on

conservative treatment, another 45 haemodialysis patients and 45 healthy controls fulfilling the selection criteria. Antibody titer of Covid-19 vaccine was measured before and 14 days after 1st dose of vaccination.

In this present study, the mean age was 49.71 $\pm$ 12.99 years in CKD 4, 5 on conservative treatment, 48.65 $\pm$ 14.61 years in MHD and 40.08 $\pm$ 11.17 years in control. More than half of the patients were male in both groups, which is consistent with a study done by Shahin *et al.*, (2009). It was observed that more than half (56.1%) of patients belonged to age was  $\leq 50$  years in CKD, 22(55.0%) in MHD and 30(76.9%) in control.

Regarding the comparison of BMI with study groups, it was observed that almost half (46.3%) of patients belonged to BMI was normal in CKD 4, 5 on

conservative treatment, 16(40.0%) in MHD and 29 (74.4%) in control (Table II). The Similar range of BMI in these group of patients was observed by Kataoka *et al.*, (2019) and Ahmed *et al.*, (2021). The differences of BMI were statistically significant ( $p < 0.05$ ) among three groups and it was less in CKD 4, 5 on conservative treatment and MHD groups than in controls group. This may be due to wasting is prevalent among patients with chronic kidney disease and this was thought to be the direct consequence of inadequate nutrition intake or malnutrition. Other factors including systemic inflammation, influence of appetite-controlling hormones from reduced renal clearance, aberrant neuropeptide signaling, insulin and insulin-like growth factor resistance and metabolic acidosis. (Tu, Cheung and Mak, 2016).

The present study showed that around 20% study participants were seropositive before vaccination. These findings were supported by Das *et al.*, (2021), where seroconversion rate was 20.02% before vaccination, but less than that of results from Jahan *et al.*, (2021), where seroconversion rate was 22.7% which was slightly higher than our findings. Regarding comparison of pre vaccination seroconversion status with CKD 4, 5 on conservative treatment, MHD & control patients, it was observed that half 11 (50.0%) of patients had CKD followed by 8 (33.3%) had MHD and 5(20.8%) control were seropositive. In seronegative, 29(30.2%) patients had CKD 4,5 on conservative treatment, 33 (34.4%) had MHD and 34 (35.4%) control (figure 3). It was observed that more participants with CKD 4, on conservative treatment and MHD become seropositive than controls although they were asymptomatic. On top of that, the vast majority of these vulnerable patients are treated with in-center haemodialysis. This means an increased risk of exposure to COVID-19 due to the frequent contacts with potentially infected patients, health care professionals or transport personnel (Baden *et al.*, 2021). Also, these patients have several conditions that make them a target population for the virus, i.e., an older age, comorbidities and a frail immunological system (Vivanco-Hidalgo *et al.*, 2020). On observation of antibody titers, the mean antibody titers in 2nd sample (14 days after 1st dose of vaccination) was  $227.66 \pm 225.82$  in CKD 4, 5 on conservative treatment,  $168.27 \pm 165.73$  in MHD and  $334.07 \pm 54.35$  in control. Among CKD stage 4, 5 on conservative management group 90.04% patients had positive immune response whereas in MHD group 84.82% responded to vaccination and immune response in control group was 100% (Table III). On the other hand, Sanders *et al.*, 2022, showed that after the 1st dose vaccination, the seroconversion rate was 100% in controls, whereas it was 93.54% and 87.4% in the CKD 4, 5 on conservative management group and MHD group. Another study showed that all subjects in the control group developed a positive antibody response (defined as 50 AU/ml or higher) as compared with 96% (54 of 56) in the dialysis group. The two patients with no serologic response were a 75-year-old man with long-

term immunosuppression (low-dose prednisone), diabetes mellitus, and hypertension and a 90-year-old diabetic man (Grupper *et al.*, 2021). So, patients with CKD 4, 5 on conservative management and on MHD had less antibody titers than control group. This means a significant portion of MHD patient may remain unprotected, despite 1st dose of vaccination. This may be due to patients with CKD 4, 5 on conservative management and receiving hemodialysis have significant degree of inflammation, malnutrition and uremia, which impair antigen presentation and T cell activation and finally there is reduced antibody production, thus a single dose vaccination is not sufficient for protection (Nahar *et al.*, 2011).

The mean antibody titer of 3rd sample (14 days after the 2nd dose of vaccination) was  $396.02 \pm 93.24$  in CKD 4, 5 on conservative management,  $318.84 \pm 54.49$  in MHD and  $604.29 \pm 150.28$  in control. Immune response is 100% among all the groups after vaccination but the concentration of antibody differs significantly among the study groups (Table IV). These findings were supported by Sanders, *et al.*, (2022). Where the seroconversion rate at day 28 after the second vaccination which was 100% seroconversion rate in the control cohort ( $P < 0.001$ ). Another study results revealed that in patients with CKD 4, 5 on conservative management and dialysis patients, the seroconversion rates were 100% and 99.4%, respectively, which the latter not statistically different from that in controls. After the second vaccination, anti-SARS-CoV-2-S (Spike) IgG levels were found to be positive in all CKD 4, 5 patients 4, 5 on conservative management (100%), and 69 of 70 HD patients (98.5%) (Paalet *et al.*, 2021). So, antibody response in CKD 4, 5 on conservative treatment and dialysis patients is not inferior to that of controls at 28 days after the second dose of vaccination but antibody levels were much lower than the control groups. Although dialysis patients had marginally reduced antibody level despite their average kidney function much lower than CKD 4, 5 patients on conservative management. This indicate dialysis is an important determinant factor for antibody response. These findings may be due to the weak immune response to vaccination in dialysis patient, both in terms of seroconversion frequency and the absolute IgG level which are usually related to renal pathologies. Another study showed that, in dialysis patients, older age, current immune-suppressive therapy or chemotherapy, lower serum albumin, lower white blood cell or lymphocyte counts, lower hemoglobin and lower dialysis adequacy were identified as indicators of a lower antibody response or non-response. On the other hand, younger age, higher serum albumin, lower intravenous iron dose, body mass index  $< 30$  kg/m<sup>2</sup>, HBV vaccine antibody response  $> 20$  IU/mL, higher Kt/V urea value were correlated with higher seroconversion rates (Attias *et al.*, 2022).

When stratified by clinical and laboratory variables, this current study showed a lower response in

older adults, obese, advanced CKD patients specially on dialysis. It was observed that when comparing the groups and data within groups, age is a substantial factor in determining the level of response. Following increasing age, there was significant decrease of antibody levels in all samples. Similar findings were observed by Grupper *et al.*, (2021). Where they observed older age was associated with antibody response in the lower quartile. This can partially be explained by a reduction in immunologic memory with increasing age as aged T cells produce short lived inflammatory effector T-cells instead of memory or follicular helper T cells (Akyol *et al.*, 2021). As degeneration of bone marrow occurs with aging, impairment of humoral and cellular immune response occurs. As a result, there is less seroconversion following vaccination in old age (Asan *et al.*, 2017).

Regarding observation of BMI in relation to immune response, it was found that patients having BMI either underweight or obese had lower immune response than normal. In the current study, three fourth (75.8%) of patients who had adequate response had normal range of BMI. Patients with BMI either underweight & obese did not achieve adequate response, there were more non responders. The differences of BMI were statistically significant ( $P < 0.05$ ) within different immune response groups (Table VIII). Al Saran *et al.*, (2021) stated that there was no significant difference in BMI among response groups, which did not support our study. But Asan *et al.*, (2022) stated that BMI  $\geq 30$  kg/m<sup>2</sup> has a significant association with non- response to SARS-COV-2 vaccination. There may be multiple reasons behind this reduced immune response in obese - the amount of SARS-COV-2 in the vaccine may be too low in relation to body mass, suboptimal immune dysfunction in obese population due to hyperinsulinemia and hyperlipidemia and may be needles were too short to reach the muscle (Meier and Berger, 2020). This present study showed malnutrition was also associated with poor immune response and among MHD patients there were more underweight patients than CKD.

In comparison to prevaccination antibody titers with post vaccination antibody titers among the study groups, the mean 2nd sample was  $341.42 \pm 41.67$  in seropositive and  $313.86 \pm 46.35$  in seronegative. The mean 3rd sample was  $469.36 \pm 127.77$  in seropositive and  $391.46 \pm 96.16$  in seronegative. The differences of 2nd sample and 3rd sample were statistically significant ( $p < 0.05$ ). Regarding immune response in seropositive populations reveals that antibody levels are more in seropositive than in seronegative patient in 2nd and 3rd sample and there is a significant difference among the antibody levels. These findings were supported by Talaei *et al.*, (2022), which showed that there were increasing trend of antibody titers in prevaccination seropositive patient. The increasing trend of antibody may be due to asymptomatic infection. Another study suggested that a previous SARS-CoV-2 infection had a booster effect on the intensity of antibody response (in high responder).

They showed that an initial encounter with the virus helps trigger a secondary broad immune response to the antigen which makes a link between seroconversion rate and the IgG levels (Bachelet *et al.*, 2021).

## CONCLUSION

This study showed that the early and long- term antibody response is highly variable both in quantity and duration. Even if vaccination was followed by a seroconversion, the antibody concentration was significantly lower in patients with CKD 4, 5 on conservative management and MHD than in control subjects. As a result, most of them remains unprotected despite having scheduled vaccination.

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