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Medicine

An Observational Study: SARS-CoV-2 Vaccination Response in Chronic Kidney Disease Patients on Dialysis

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Abstract **Original Research Article**

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 1st 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 1st dose of vaccination the 2nd samples were taken, 3rd samples were taken 14 days after the 2nd dose vaccination and 4th sample was taken 6 months after the 2nd dose of 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 quantitive antibody response; positive response- values ≥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 1st 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 2nd dose of vaccination but the concentration of antibody differs

significantly among the study groups. Antibody response after 6 months completion of 2nd dose of vaccination reveals that, among CKD stage 4, 5 on conservative management group 80.3% patients had immune response whereas in MHD group 67.2% responded to vaccination but immune response in control group was 100%. 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 measurement mainly 6 months after vaccination compared to controls, supports the need for booster vaccinations to foster a stronger and more persistent antibody response.
Key Words: Covid-19, Corona virus, CKD, MHD.

INTRODUCTION

The emergence of coronaviruses in 1966 marked the beginning of an intricate relationship between these enveloped, positive, single-stranded large RNA viruses and various species, including humans. However, the pivotal turn arrived with the advent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the unprecedented coronavirus disease 2019 (COVID-19). This novel virus, first identified amidst an outbreak in Wuhan City, China, catapulted into a spectrum of clinical manifestations, spanning from mild respiratory issues to life-threatening complications such as severe pneumonia and even mortality.

Amidst this panorama, populations with pre-existing health conditions faced disproportionate risks, especially those with chronic kidney disease (CKD). A global health burden, CKD's prevalence surged to alarming figures, leading to increased mortality rates and emerging as a significant cause of death worldwide. For those progressing to end-stage kidney disease (ESKD), necessitating renal replacement therapies like dialysis, vulnerabilities to infections were compounded, particularly in the wake of the COVID-19 pandemic.

The convergence of COVID-19 and CKD not only spotlighted the susceptibility of this patient cohort but also underscored the challenges in vaccination responses due to immune system dysregulation inherent in CKD. This intricate interplay, evident in previous vaccinations against other diseases, illuminates the nuanced landscape of immunosuppression and its impact on vaccination efficacy in CKD patients.

Amidst this complex backdrop, the rapid development and deployment of vaccines against SARS-CoV-2 offered a glimmer of hope, yet revealed intriguing nuances in vaccine efficacy over time. The meticulous examination of vaccine response among dialysis patients sheds light on the multifaceted dynamics of immune response, unveiling the hurdles and possibilities in mitigating the impact of COVID-19 within this vulnerable population.

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:

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	%	
Age (years)							
≤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		[a]0.085[ns]
Range (min-max)	27-76		24-78		23-63		
Sex							
Male	21	51.2	21	52.5	25	64.1	[b]0.445[ns]
Female	20	48.8	19	47.5	14	35.9	

ns= not significant
[a]p value reached from Kruskal Wallis test
[b]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.

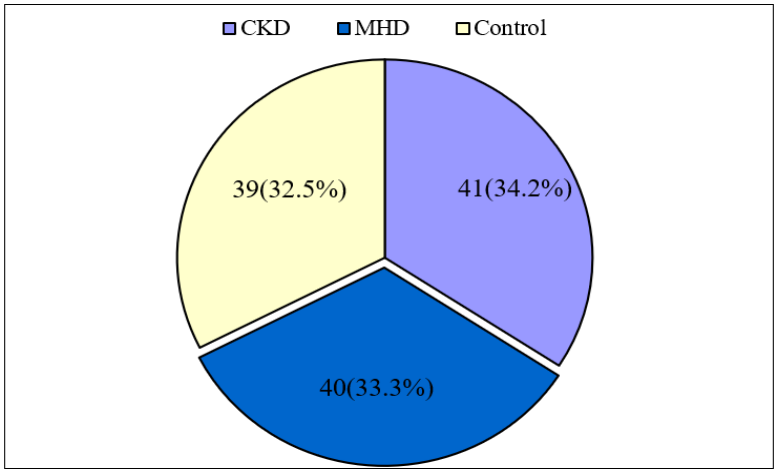

Figure 1: Pie chart shows the CKD, MHD and control status of study patients (n=120)

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

BMI (kg/m^2)	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		[a]0.007[s]

s= significant ns= not significant
[a]p value reached from ANOVA test
[b]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^2 in CKD, 22.1±2.1 kg/m^2 in MHD and 24.3±3.7 kg/m^2 in control. The differences of BMI were statistically significant (p<0.05) among three groups.

Table III: Comparison of causes of CKD with study groups (N=120)

Cause of CKD	CKD stage- 4, 5 (n=41)		MHD (n=40)		Control (n=39)		*p* value
	n	%	n	%	n	%	
Glomerulonephritis	14	34.1	12	30.0	0	0.0	0.001^s
Diabetes mellitus	15	36.6	14	35.0	0	0.0	0.001^s
Hypertension	5	12.2	6	15.0	0	0.0	0.049^s
Others	4	9.8	5	12.5	0	0.0	0.086^{ns}
Unknown	3	7.3	4	10.0	0	0.0	0.152^{ns}

s= significant
ns= not significant
p value reached from Chi-square test

Table III shows the comparison of cause of CKD with study groups. Glomerulonephritis, diabetes mellitus and hypertension were statistically significant (p<0.05) among three groups.

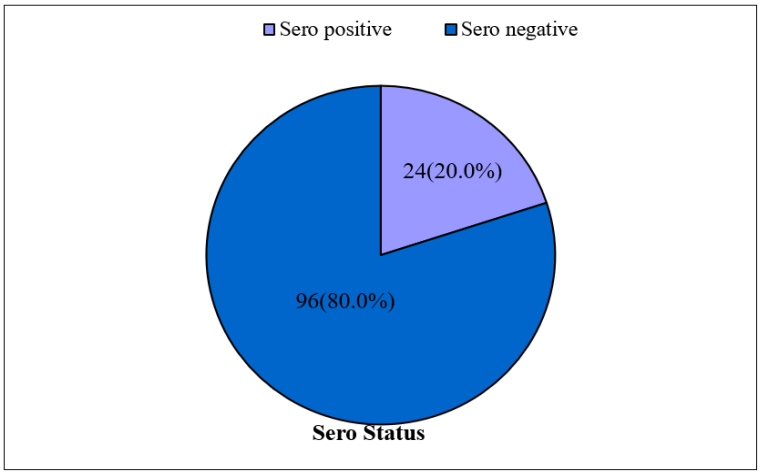

Figure 2: Pie chart shows the pre vaccination seroconversion status of study population (n=120)

Pie chart shows the pre vaccination seroconversion status of study population. It was observed that about one fourth (20.0%) of patients was seropositive and 96 (80.0%) were seronegative.

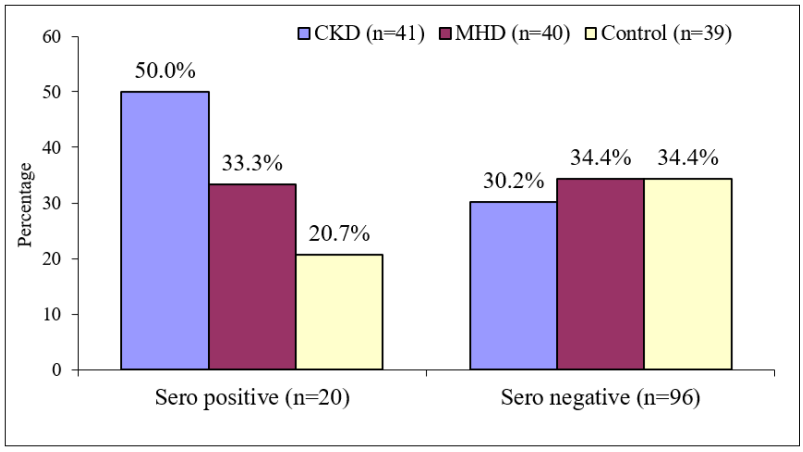

Figure 3: Bar diagram shows the Comparison of pre vaccination seroconversion with CKD, MHD & control patients (n=120)

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 IV: 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	
2nd sample (14 days after 1st dose	341.42±41.67	223.86±46.35	0.001^{s}
3rd sample (14 days after 2nd dose)	469.36±127.77	291.46±96.16	0.001^{s}
4th sample (6 months after 2nd dose)	243.37±61.89	121.59±46.81	0.001^{s}

s= significant ns= not significant
p value reached from Unpaired-t test

Table IV shows the comparison of pre vaccination seroconversion status with Anti-body titers. The mean 2nd sample was 341.42±41.67 in seropositive and 223.86±46.35 in seronegative. The mean 3rd sample was 469.36±127.77 in seropositive and 291.46±96.16 in seronegative. The mean 4th sample was 243.37±61.89 in seropositive and 121.59±46.81 in seronegative. The differences of 2nd sample, 3rd sample and 4th sample were statistically significant (p<0.05) with pre vaccination seroconversion status.

Table V: 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	
1st sample (pre vaccination)	31.5±26.41	29.48±23.79	43.21±41.61	0.298^{ns}
2nd sample (14 days after 1st dose)	227.66±225.82	168.27±165.73	334.07±54.35	0.001^{s}
3rd sample (14 days after 2nd dose)	396.02±93.24	318.84±54.49	604.29±150.28	0.001^{s}
4th sample (6 months after 2nd dose)	187.81±180.86	126.03±117.8	388.33±70.11	0.001^{s}

s= significant
ns= not significant
p value reached from ANOVA test
CKD= Chronic kidney disease MHD= Maintenance hemodialysis

Table V shows the comparison of Anti-body titers with study groups. The mean 1st 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 2nd sample was 227.66±225.82 in CKD, 168.27±165.73 in MHD and 334.07±54.35 in control. The mean 3rd sample was 396.02±93.24 in CKD, 318.84±54.49 in MHD and 604.29±150.28 in control. The mean 4th sample was 187.81±180.86 in CKD, 126.03±117.8 in MHD and 388.33±70.11 in control. The differences of 2nd, 3rd and 4th sample mean were statistically significant (p<0.05) among three groups.

Table VI: 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	
1st sample (pre vaccination)	30.5±27.41	29.18±17.08	0.298^{ns}
2nd sample (14 days after 1st dose)	220.66±215.62	203.78±195.73	0.241^{s}
3rd sample (14 days after 2nd dose)	380.52±74.24	365.84±56.49	0.231^{s}
4th sample (6 months after 2nd dose)	180.81±175.86	156.03±150.8	0.261^{s}

s= significant
ns= not significant
p value reached from ANOVA test
CKD= Chronic kidney disease

Table VI shows the comparison of Anti-body titers with CKD- 4,5. The mean 1st sample (pre vaccination) was 30.5±27.41 in CKD and 29.18±17.08 in CKD-5. The mean 2nd sample was 220.66±215.62 in CKD-4 and 203.78±195.73 in CKD-5. The mean 3rd sample was 380.52±74.24 in CKD-4 and 365.84±56.49 in CKD-5. The mean 4th sample was 180.81±175.86 in CKD-4 and156.03±150.8 in CKD-5. The differences of 2nd, 3rd and 4th sample mean were not statistically significant (p<0.05).

Table VII: Antibody titers after 14 days of completion of 1st dose of vaccination (2nd 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
Responder (108) (≥10 DU/ml)	36 (90.04%)	33 (84.82%)	39(100%)	0.046[s]
Non-Responder (12) (<10 DU/ml)	5 (12.19%)	7 (21.21%)	0	
Antibody titer (DU/ml) (Mean ± SD)	227.66±225.82	168.27±165.73	334.07±54.35	0.001[s]

s= significant p value reached from ANOVA test
CKD= Chronic kidney disease MHD= Maintenance hemodialysis

Table VII shows the antibody titers after 14 days of completion of 1st 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 VIII: 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
Responder (120) (≥10 DU/ml)	41 (100%)	40 (100%)	39 (100%)	----
Non-Responder (0) (<10 DU/ml)	0	0	0	
Antibody titer (DU/ml) (Mean ± SD)	396.02±93.24	318.84±54.49	604.29±150.28	[b]0.001[s]

s= significant [a]p value reached from Chi-square test
[b]p value reached from Kruskal Wallis test

Table VIII shows the antibody titers after 14 days of completion of 2nd 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 IX: Comparison of immune response according to age of study population (n=120)

Age in years	1st sample (pre vaccination)	2nd sample (14 days after 1st dose	3rd sample (14 days after 2nd dose)	4th sample (6 months after 2nd dose)	P value
	Mean±SD	**Mean±SD**	**Mean±SD**	**Mean±SD**	
≤50 years	30.65±41.39	324.6±47.48	441.36±126.71	265.7±414.12	0.001[s]
51–70 years	30.06±44.7	322.63±43.77	414.52±121	208.15±42.2	0.001[s]
> 70 years	15.42±41.34	238.22±44.18	295.53±72.63	137.07±648.04	0.001[s]

s= significant
P value reached from Kendall's W Test

Table IX shows the association between age with anti-body titers. The ages level of ≤50 years, 51-70 years and > 70 years were statistically significant ($p<0.05$) with anti-body collection groups

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

Variables	Responder (≥10 DU/ml)	Non-Responder (<10 DU/ml)	*p* value
BMI (Kg/m^2)			
Underweight (11)	-	(30.3%)	
Normal (64)	(75.8%)	(44.8%)	
Overweight (33)	(24.2%)	(21.3%)	
Obese (12)	-	(3.6%)	
Mean ± SD	23.1±3.1	20.0±3.2	[a]0.018[s]

s= significant ns= not significant [a]p value reached from Unpaired-t

Table X shows the immune response to SARS-COV-2 vaccination in relation to BMI (Kg/m^2). 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 aimed to analyze the antibody response elicited by SARS-CoV-2 vaccines in three distinct groups: healthy individuals, patients with chronic kidney disease (CKD) stages 4 and 5 undergoing conservative management, and those on maintenance hemodialysis (MHD). The prospective observational comparative study included 45 patients in each group. Antibody titers were assessed before and after vaccination, with measurements taken at various intervals up to 6 months post the second vaccine dose.

In our investigation, the mean ages were 49.71±12.99 years for CKD stages 4 and 5 on conservative treatment, 48.65±14.61 years for MHD, and 40.08±11.17 years for healthy controls. Gender distribution reflected similar proportions across the groups, aligning with previous studies by Shahin *et al.*, (2009). The body mass index (BMI) comparisons revealed significant differences among the groups, with lower BMIs observed in CKD stages 4 and 5 and MHD groups compared to the control group. This disparity might be attributed to prevalent wasting seen in CKD patients, driven by factors such as inadequate nutrition intake, systemic inflammation, altered appetite-controlling hormones, and metabolic disturbances.

Before vaccination, approximately 20% of the study participants were seropositive, in line with findings from other studies by Das *et al.,* (2021) and Jahan *et al.*, (2021). Analysis of pre-vaccination seropositivity showed a higher rate in CKD and MHD patients compared to controls. Notably, despite being asymptomatic, a considerable number of CKD and MHD patients tested seropositive, potentially due to increased exposure risks during frequent hospital visits and their immunologically vulnerable state.

Following the first vaccine dose, antibody titers were notably lower in CKD stages 4 and 5 and MHD groups compared to controls, corroborating findings from Sanders *et al.,* (2022) and Grupper *et al.,* (2021). This suggests that a single vaccine dose might not offer sufficient protection to these patient groups due to underlying inflammation, malnutrition, and impaired immune responses associated with CKD.

After the second vaccine dose, while all groups exhibited immune responses, CKD stages 4 and 5 and MHD patients showed significantly lower antibody titers compared to controls. This implies that although these patient groups developed an immune response, their antibody levels remained notably lower than those in healthy individuals. At the 6-month mark post-vaccination, CKD stages 4 and 5 patients on conservative treatment and MHD patients exhibited reduced immune responses compared to controls. This aligns with studies by Berer *et al.,* (2021), Agur *et al.,* (2022), and Sanders *et al.*, (2022), indicating a decline in antibody titers over time, potentially due to uremia- induced immune dysregulation affecting both immune depression and activation.

Factors influencing lower responses included older age, higher BMI (especially in the underweight and obese categories), and possible malnutrition. These findings echo observations by Grupper *et al.*, (2021) and Al Saran *et al.,* (2021). Advanced CKD patients on dialysis demonstrated notably reduced immune responses compared to CKD patients on conservative management, potentially due to factors such as inflammation, decreased immune function, and the impact of dialysis on immune responses.

Additionally, patients with prior seropositivity showed stronger antibody responses following vaccination, suggesting that prior exposure to the virus might enhance the immune response, as noted in studies by Talaei *et al.*, (2022) and Bachelet *et al.*, (2021).

CONCLUSION

This study showed that the early and long- term antibody response varied considerably in both quantity and duration among the studied groups. Despite observing seroconversion following vaccination, patients with CKD stages 4 and 5 undergoing conservative management and those on MHD exhibited significantly lower antibody concentrations compared to control subjects. Consequently, the majority of these patients remain unprotected despite receiving scheduled vaccinations.

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