

Prevalence of anti-SARS-CoV-2 antibody in hemodialysis facilities: a cross-sectional multicenter study from Madinah

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BACKGROUND: Since the occurrence of coronavirus disease in 2019 (COVID-19), the global community has witnessed its exponential spread with devastating outcomes within the general population and specifically within hemodialysis patients.

OBJECTIVES: Compare the state of immunity to SARS-CoV-2 among hemodialysis patients and staff.

DESIGN: Cross-sectional study with a prospective follow-up period.

SETTING: Hemodialysis centers in Madinah region.

PATIENTS AND METHODS: We prospectively tested for SARS-CoV-2 antibodies in dialysis patients using dialysis centers staff as controls. The participants were tested on four occasions when feasible for the presence of anti-SARS-CoV-2 antibodies. We also analyzed factors that might be associated with seropositivity.

MAIN OUTCOME MEASURES: SARS-CoV-2 positivity using immunoglobulin G (IgG) levels

SAMPLE SIZE: 830 participants, 677 patients and 153 dialysis centers staff as controls.

RESULTS: Of the total participants, 325 (257 patients and 68 staff) were positive for SARS-CoV-2 IgG antibodies, for a prevalence of 38.0% and 44.4% among patients and staff, respectively ($P=0.1379$). Participants with a history of COVID-19 or related symptoms were more likely to have positive IgG ($P<0.0001$). Surprisingly, positivity was also center-dependent. In a multivariable logistic regression, a history of infection and related symptoms contributed significantly to developing immunity.

CONCLUSION: The high prevalence of SARS-CoV-2 antibody among hemodialysis patients and previously asymptomatic staff suggested past asymptomatic infection. Some centers showed more immunity effects than others.

LIMITATIONS: Unable to collect four samples for each participant; limited to one urban center.

CONFLICT OF INTEREST: None.

In December 2019, a respiratory illness similar to the 2004 outbreak of severe acute respiratory syndrome coronavirus 1 (SARS-1) was documented in many patients in Wuhan City, Hubei Province, China.¹ The pathogen was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease coronavirus disease 2019 (COVID-19).² In January 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern with subsequent declaration of the COVID-19 pandemic.³

Since its occurrence, COVID-19 has affected individuals in every country.⁴ As of July 2022, the number of cases exceeded 800,000 in Saudi Arabia.⁵ COVID-19 has affected individuals of all ages; however, higher death rates are reported in vulnerable individuals such as the elderly and those with multiple comorbidities.⁶ The dialysis patient population is inherently immunocompromised and is at high risk of developing a severe or fatal disease. A death rate of more than 10% has been reported in COVID-19 patients receiving hemodialysis.^{7,8} Despite curfew and lockdown measures, maintenance hemodialysis (MHD) patients are required to visit dialysis facilities multiple times a week for regular treatment, which poses a challenge in addressing the spread of infection among this population.⁹

Several publications on dialysis patients have reported challenges in treatment during this pandemic.^{10,11} However, there have been no reports on the local experience in Saudi Arabia in terms of the incidence and outcome of COVID-19 disease in hemodialysis patients. Understanding the patterns of disease is essential to delivering proper care to the country's dialysis population. This understanding will also help identify the risks associated with severe infections and mortality among this patient group. It is also important to address the impact on the spread of COVID-19 disease within the community through the movement of asymptomatic dialysis patients during frequent visits to the dialysis units.¹² Clarke et al have reported higher rates of asymptomatic disease among dialysis patients compared with the general population.¹³ This observation increases the likelihood of silently spreading the infection since they would have higher false-negative visual screening. This dormancy, in turn, would increase the exposure to other patients and workers in health facilities, and significantly increase the spread of COVID-19 disease, especially in the absence of proper infection control precautions. Also, there is the possibility of presenting late with severe disease and increased risk of morbidity and mortality.

An increasing number of publications have shown

the value of antibody testing, alone or combined with PCR-based testing, in diagnosing SARS-CoV-2 infection.^{14,15} However, it remains unclear whether this benefit is similar in hemodialysis populations. The financial costs incurred by dialysis centers are staggering, which has restricted operations at dialysis facilities. Under the circumstances, it is crucial to investigate the nature, dynamics, transmission, immunity, and disease patterns of COVID-19 in the hemodialysis population in Saudi Arabia during this pandemic. The study's null hypothesis was that there is no difference in the seroprevalence of SARS-CoV-2 among patients and the general population (represented by staff).¹⁶ The aim was to evaluate the immunity patterns and differences among maintenance hemodialysis patients and staff.

PATIENTS AND METHODS

In this cross-sectional study with prospective follow up we aimed to evaluate the SARS-CoV-2 antibodies status among patients in the Madinah region of Saudi Arabia, including dialysis patients and staff from the same dialysis centers as the study controls at a 4:1 ratio. The main objectives were to evaluate the state of immunity to SARS-CoV-2 virus among maintenance hemodialysis (MHD) patients and staff working at the same facilities and compare the seroprevalence within the two groups, and describe the clinical features attributed to COVID-19. Besides being patient or staff, participants had to be older than 18 years and able to provide informed consent. After consents were signed, data was obtained via electronic case report forms. The Ministry of Health IRB approved the study; central IRB log No. 20-126M, on June 30, 2020. Patients receiving other forms of dialysis (i.e., non-hemodialysis), transient patients, and non-permanent staff were excluded. Participants were tested monthly (up to four times) for the presence of SARS-CoV-2 antibodies during a 12-week follow-up period. An adverse event reporting plan was created to cover all possible minimal side effects. All possible side effects and the importance of reporting any signs to the responsible study team member during the whole study period were clearly explained to each participant.

The study targeted all hemodialysis centers in Madinah city, covering approximately 1000 patients and 250 staff. Given the manageable size of the target population, we aimed to include all eligible candidates. However, to ensure including the minimum number of participants, we performed a formal sample size calculation a priori. Based on the available literature, we estimated a 25% seroprevalence in the general population.^{16,17} To detect a minimum difference of 40% in the

seroprevalence between the dialysis population and staff, we used a chi-square test for population proportions. We considered a significance level of .05 (two-tailed) and statistical power of .8.¹⁸ Accordingly, our estimated minimum sample size to detect the selected difference was 620 patients and 155 controls (staff).

According to the study plan, electronic case report forms were designed to collect data from all participants.¹⁹ Data were automatically stored in a secured online space to maintain data integrity and accidental loss issues. Most of the attributes were chosen from the provided list in the electronic case report form, except the participant's name, identification (ID), and date of birth to avoid human error. The collected data were re-validated to ensure its quality at all stages during the study period. Collected data included demographic, laboratory information, dialysis center, dialysis shifts, comorbidities, COVID-19 infection status, symptoms, and hospitalization. Demographic information was collected from the center's information system, and the laboratory information was provided by the Ministry of Health's (MOH) central lab in King Fahad General Hospital, MOH information systems, and the Health Electronics Surveillance Network system. Symptoms related to COVID-19 and information about outcomes were obtained directly from recovered COVID-19 patients in MHD centers and their medical records. After recruitment, information on operating practices (facility layout and processes, staff schedules, patient schedules) was obtained via the facility information system. Blood samples were collected from all the participants following the standard protocol, and IgG antibodies were measured using the SARS-CoV-2 total antibodies IgG assay kit (Abbott Diagnostics, US). The value of antibodies was observed among the participants to see their immunity patterns during 90 days of the study period, and multiple tests (maximum 4) were performed to maximize the likelihood of capturing positive results in immune patients. BEP III system (Siemens Healthcare Diagnostics) was used to measure the amount of IgG in the samples. A validation test for the used kits was performed before analyzing the samples. We used the commercial SARS-CoV-2 IgG and IgM Enzyme Linked ImmunoSorbent Assay (ELISA) Kit (BGI Europe A/S) which targets the S-gene (spike protein) (catalog number 0601038). To minimize the effect of temporal variation of seroconversion, we designed the study to include a total of four blood tests from each participant at monthly intervals. We also noted the dialysis facility's ID to analyze the variation in seroprevalence between facilities. A serum ratio of ≥ 1 was considered positive. Participants were also evaluated for the presence of

symptoms, including fever, tachycardia, and hypoxemia. The evaluation included a history of COVID-19, associated symptoms, complications, and severity.

The primary outcome was the dichotomous (positive and negative) SARS-CoV-2 IgG antibody status. Patients labelled positive had a positive antibody result at least once during the study period. Chi-square statistics were used to compute *P* values for categorical data with the threshold set at .05 as the level of significance. Statistical comparisons were performed between all variables and IgG antibody results to evaluate the significance to assess development of immunity. The odd ratios for an individual variable and the IgG values were also computed. To further support the *P* value calculations, Cohan's kappa and Matthew's correlation coefficients (not presented) were computed to measure the inter-rater reliability for the categorical data. Univariate analysis was used to select variables for multivariable logistic regression to compute adjusted odd ratios. ANOVA, chi-square, recursive feature elimination, and recursive feature elimination with cross-validation approaches were used to find the best combination of variables for the final selection. We used multiple logistic regression analysis to evaluate the relationship between SARS-CoV-2 seropositivity (dependent variable) and factors that might be associated with seropositivity. The open-source Python packages 'scipy', 'statsmodels', and 'scikit-learn' were used for all statistical analysis. Where needed, custom modules were created using Python for the analysis.

RESULTS

Participants included 677 patients (out of 692) and 153 staff who were eligible and enrolled in this study. Per study protocol, we aimed to collect 3320 samples (four samples from each participant). However, since not all patients ended up providing four samples as planned, we finally collected 2735 samples (**Figure 1**). This mismatch was either due to participants' refusal to provide samples or their absence on the sample collection day. Furthermore, 15 participants (not shown in Figure 1) were excluded from the analysis because of kidney transplant ($n=5$), death ($n=3$), and withdrawal for personal reasons ($n=7$).

The median and range of ages of patients and staff differed considerably and hospitalization rates were higher among dialysis patients (**Figure 2**). Similar proportions of patients and staff were positive for SARS-CoV-2 antibodies (**Table 1**). As shown in **Table 1**, the COVID-19 disease hospitalization rate was high among the patients, (11.2% vs 0.65%). Seventy-seven participants (11.4%), including one staff member, were hos-

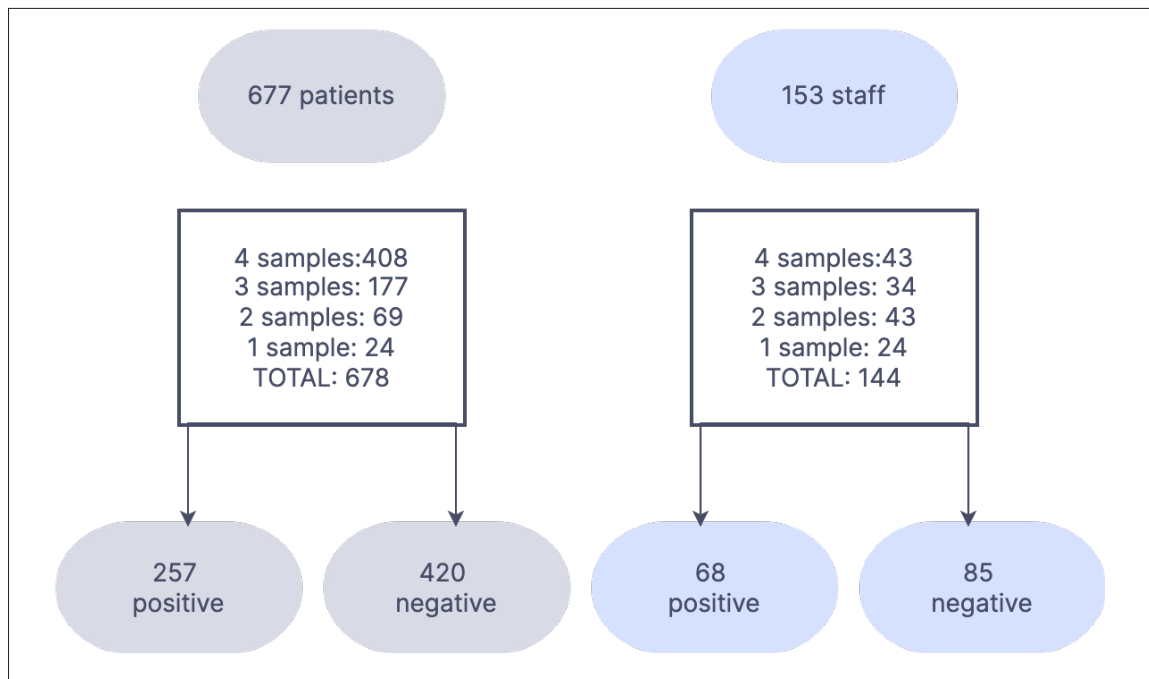


Figure 1. Study flow diagram.

pitalized because of COVID-19. Common symptoms were cough, fever, sore throat, fatigue, runny nose, and muscle pain but diarrhea, insomnia, chills, vomiting, headache and joint pain were very rare.

In the multivariate logistic regression (**Table 2**), seropositivity was associated with symptoms and a history of symptoms, testing by nasopharyngeal swab and hospitalization. Staff or patient status was not significant as

indicated in the univariate analysis.

Most hospitalized patients were reported in one center, Center 2 (57/76, 75% hospitalized) (**Figure 3**). Fifty percent (38/76) of the hospitalized patients did not test positive for IgG antibodies. The one staff member who was hospitalized was not in Center 2. Most of the hospitalized patients had a history of smoking and were seronegative (75% of hospitalized patients were smokers and 50% of the total hospitalized were seronegative).

Most participants provided all four samples, which helped us identify unique immunity patterns based on the IgG outcomes. Patients and staff were either negative for all four tests, positive for all four, or had negative and then a final positive test, or had positive tests and a final negative test.

DISCUSSION

Seroprevalence did not differ between dialysis patients and staff in this study and the percentages for positivity were greater than in other studies, probably because the study is recent.^{13,20} Our study revealed that symptoms and history of COVID-19 disease among patients and staff were significantly associated with seropositivity (*P* values <.0001 with odds ratios of 1.7 and 4.7, respectively). Adjusted odds ratios showed a higher likelihood of the participant being IgG positive with past COVID-19 history, and COVID-19 symptoms. Most

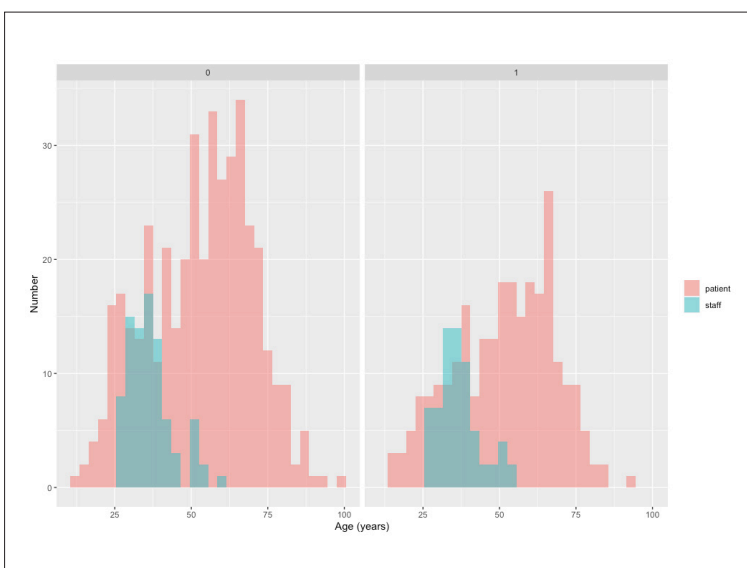


Figure 2. Ages of participant groups by IgG results (0=negative, 1=positive) (*P*<.0001).

Table 1. Baseline characteristics of the study population

	Patients			Staff (Controls)			P value
	Total patients (n=677)	Positive antibodies (n=257, 38.0)	Negative antibodies (n=420)	Total staff (n=153)	Positive antibodies (n=68, 44.4)	Negative antibodies (n=85)	
Age (years)	54 (26)		35 (8)				<.001
Gender							
Female	323	117	206	74	34	40	.883
Male	354	140	214	79	34	45	
Smoking history	133 (19.7)	53 (20.6)	80 (19.0)	22 (14.4)	10 (14.7)	12 (14.1)	.1311
Hypertension	554 (81.8)	209 (81.3)	345 (82.1)	8 (5.2)	5 (7.4)	3 (3.5)	.039
Diabetes	261 (38.6)	97 (37.7)	164 (39.0)	0	0	0	.632
Had COVID-19 symptoms	113 (16.7)	64 (24.9)	49 (11.7)	28 (18.30)	19 (27.9)	9 (10.6)	<.001
Hospitalized for COVID-19	76 (11.2)	38 (14.8)	38 (9.0)	1 (0.65)	1 (1.5)	0	.138

Data are n (%) and median (interquartile range) for age.

Table 2. Multivariable logistic regression analysis with SARS-CoV-2 seropositivity as dependent variable.

Variable/Feature	Total Participants (830)	Positive IGG (325)	Negative IGG (505)	P value	Odd ratio	Adjusted Odd ratio	CI
COVID-19 history	68 (8.19%)	55 (16.92%)	13 (2.57%)	<.0001	7.709	4.489542	(0.0633, 0.1006)
COVID-19 symptoms	141 (16.99%)	83 (25.54%)	58 (11.49%)	<.0001	2.643	1.671090	(0.1443, 0.1954)
Nasopharyngeal swab	457 (55.06%)	210 (64.62%)	247 (48.91%)	<.0001	1.907	1.450206	(0.5168, 0.5844)
Hospitalized for COVID-19	77 (9.28%)	39 (12.0%)	38 (7.52%)	.0301	1.676	1.317071	(0.073, 0.1125)
Nurse	98 (11.81%)	47 (14.46%)	51 (10.1%)	0.0573	1.505	1.572480	(0.0961, 0.14)
Dialysis shift	341 (41.08%)	138 (42.46%)	203 (40.2%)	0.5177	1.098	1.247601	(0.3774, 0.4443)
Smoking history	155 (18.67%)	63 (19.38%)	92 (18.22%)	0.6737	1.079	0.910073	(0.1602, 0.2133)
Gender female	397 (47.83%)	151 (46.46%)	246 (48.71%)	0.5262	0.914	0.874713	(0.4443, 0.5123)
Patient vs staff	677 (81.57%)	257 (79.08%)	420 (83.17%)	0.1379	0.765	1.120584	(0.7893, 0.842)
Kidney transplant history	33 (3.98%)	10 (3.08%)	23 (4.55%)	0.2876	0.665	1.060162	(0.0265, 0.0531)
On immunosuppressive therapy	23 (2.77%)	5 (1.54%)	18 (3.56%)	0.0826	0.423	0.474299	(0.0165, 0.0389)

Intercept value: -0.8818, R²: 0.669, Adjusted R²: 0.661. The dialysis shifts were on Saturday, Monday and Wednesday.

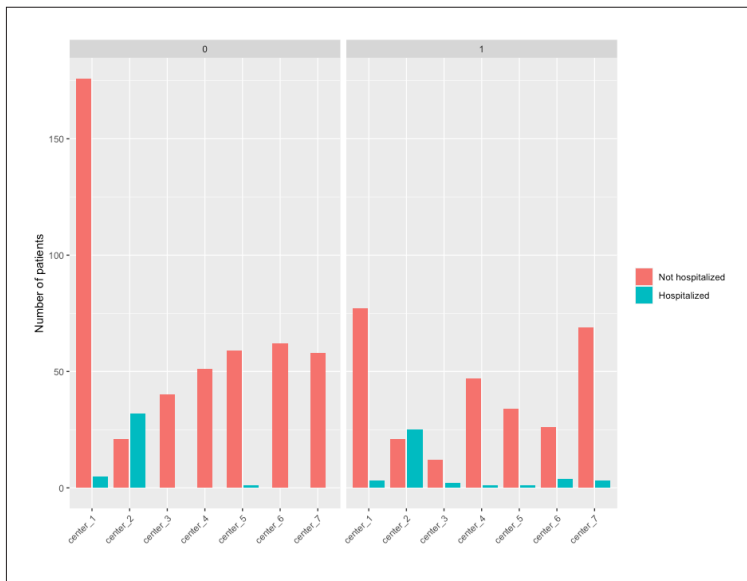


Figure 3. Hospitalization of participant groups by IgG results (0=negative, 1=positive).

of the participants reported no past COVID-19 history and no COVID-19 symptoms, but 75.1% of patients and 72.1% of staff were positive with no COVID-19 symptoms while 80.8% of patients and 85.3% staff were positive with no COVID-19 history. This high prevalence of participants in the positive antibody group suggests that a larger fraction remained asymptomatic. Similar results have also been reported among hemodialysis patients using serologic screening.^{13,21} Hemodialysis patients were at higher risk of silent infection, and one of the major sources of COVID-19 spread as they are not aware of the infection. Patients with a smoking history have shown a higher risk of hospitalization (76%) possibly because of the severity of the disease on the lungs.⁸ However, no strong connection can be established based on the available data as about 72% of hospitalizations with a smoking history were reported in only one center. The current study showed a higher seroprevalence among hemodialysis staff and the MHD patients than other groups in Saudi Arabia. In a previous study, the seroprevalence was 2.36% among healthcare workers, with a significant difference between the case-hospital (2.9%) and the control group (0.8%).²² Another study of blood donors in Saudi Arabia showed a lower prevalence seropositivity (1.4%) than the current study.²³ Different factors may have contributed to these differences, including the study population, pattern of exposure, the prevalence of COVID-19 in the community, and the timing of the study.

For the study sample size calculation, we chose to include more patients than staff for the following to improve the efficiency. First, to increase the study power by increasing the total number of participants. Including more patients was also more feasible since the number of staff is limited compared to patients. Second, the ratio of patients to staff in the selected MHD units is approximately 4:1. Therefore, including patients and staff in the same ratio will provide a proportional representation for the two groups. Third, considering the study design where a blood sample is collected on fixed dates, we have anticipated that some patients might not be sampled since the day of diagnosis would not be on a day of regular monthly blood work at the center. Including more patients in the study will likely reduce the possibility of significant loss of the follow-up (over 20% of participants). Fourth, although it has not been proven, we assumed that individual patients might vary in their immune response. Therefore, a larger number of patients would likely reduce this variability.

Limitations included the inability to collect four samples for each participant and the study was limited to Madinah city only. Expanding the study to include different regions will add more power and improve generalizability. This study included dialysis staff as a representation of the general population, raising concerns about the possibility of a healthy worker effect. Although this may be important in other epidemiological studies, we do not expect healthy staff to differ immunologically from the general population regarding SARS-CoV-2 immunity. Hence, we considered them a suitable representation for the general population. Furthermore, we believe that selecting staff exposed to the same environment as patients has the potential to neutralize any potential environmental exposure difference that may arise from comparing patients to a population from outside their facility's environment. This similarity in inpatient and staff have environmental exposure is arguably a potential strength of the study. In conclusion, among unvaccinated MHD patients and staff, we found a relatively high prevalence of SARS-CoV-2 seroprevalence in both patients and staff in Saudi Arabia dialysis facilities. This prevalence is likely indicative of the higher likelihood of exposure within hemodialysis facilities.

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