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Original Article

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Antibody Response of Coronavirus Disease 2019 Infection and Affecting Factors in Maintenance Hemodialysis Patients*

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ABSTRACT

Background: Hemodialysis patients are prone to infection due to the inadequate response of their innate and adaptive immune systems. During the early phase of the coronavirus disease 2019 (COVID-19) pandemic, hemodialysis patients had a high risk of mortality. In this study, we evaluated COVID-19 infection characteristics, seroconversion rates, related factors, and 90-day mortality after the disease in hemodialysis patients before vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods: Patients followed in outpatient hemodialysis units were included in the study. The relationships between biochemical and dialysis-related parameters of the patients, polymerase chain reaction positivity, seroconversion and mortality were examined.

Results: The prevalence of COVID-19 infection among hemodialysis patients was 15.3%. The seroconversion rate was 79.1% in 112 days. Higher C-reactive protein levels during COVID-19 infection were associated with higher SARS-CoV-2 immunoglobulin G titers (P = .014, r = 0.384) and higher parathyroid hormone levels were associated with lower antibody titers (P = .009, r = −0.375). These results were regardless of the phosphorus-lowering treatment and serum calcium or phosphorus levels. The mortality rate was 28.5%, and white blood cell count during infection was an independent risk factor for mortality (P = .004; hazard ratio = 1.451; 95% CI, 1.125-1.872).

Conclusion: In experimental studies, it has been shown that elevated parathyroid hormone adversely affects the immune response of hemodialysis patients. Our study is the first to show that the high level of parathyroid hormone negatively affects the antibody response during COVID-19 infection.

Keywords: COVID-19, chronic kidney disease—mineral and bone disorders, dialysis, secondary hyperparathyroidism, seroconversion

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INTRODUCTION

In March 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was declared a pandemic by the World Health Organization. Patients receiving maintenance hemodialysis are at risk of developing SARS-CoV-2 infection during the COVID-19 pandemic due to a lack of isolation and accompanying comorbidities. More than 762 million people in the world have been infected with the coronavirus disease 2019 (COVID-19), and more than 6.8 million of them have died, according to the data of the World Health Organization.[1] In Türkiye, more than 17 million people were affected from SARS-CoV-2 infection during the pandemic, and as stated in the Turkish Society of Nephrology 2020 registry: COVID-19 report, mortality rate was 24.4% in patients on maintenance hemodialysis.[2]

Uremia due to kidney failure results in alterations in innate immunity, like decreased bactericidal activity of neutrophils and increased but inefficient cytokine levels. Adaptive immunity is also affected and results in impaired activation of T lymphocytes, decreased number of B lymphocytes, and altered function of antigen-presenting cells.[3,4] Secondary hyperparathyroidism also causes alterations in the function of B and T cells, like elevated cytosolic calcium levels in B cells and a decrease of CD4 and CD4/CD8 ratio in T cells.[5,6] The immune system abnormalities found among patients with end-stage kidney disease lead to lower seroconversion rates after bacterial/viral infections or vaccination, which results in a lower peak and accelerated waning of antibody titers.[7]

The study aimed to determine the SARS-CoV-2-related antibody development after active infection diagnosed with SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) positivity of the nasopharyngeal swab and the factors associated with antibody development and mortality in patients on maintenance hemodialysis.

MATERIAL AND METHODS

This study was a prospective cohort study and was approved by the Baskent University Institutional Review Board and Ethics Committee (Date: January 27, 2021; Number: 21/23) and supported by University Research Fund. The study has been conducted in accordance with the principles set forth in the Helsinki Declaration.

Patients on maintenance hemodialysis treatment were included in the study. An informed consent form was obtained from patients before participation. The SARS-CoV-2 RT-PCR test was performed based on the contact and symptom status of 458 adult hemodialysis patients, which resulted positive in 70 patients.

None of the patients had passive immunity, as a vaccine against COVID-19 had not yet been developed at the start and throughout the study. Demographic characteristics, dialysis-related parameters, and the mean values of the last 6 months' biochemical and hematological parameters of all hemodialysis patients were recorded. Complete blood count, D-dimer, and inflammation markers during COVID-19 infection and death were recorded. Deaths that occur within 90 days after infection were considered SARS-CoV-2-associated mortality.

Between March 2020 and February 2021, patients on maintenance hemodialysis with COVID-19 infection diagnosed by SARS-CoV-2 RT-PCR test positivity (Diagnovital SARS-CoV-2 Multiplex RTA Laboratories Biological Products Pharmaceutical and Machinery Industry, Türkiye) were compared with SARS-CoV-2 RT-PCR-negative patients on maintenance hemodialysis.

In March 2021, the SARS-CoV-2 IgG test, which is a chemiluminescent microparticle immunoassay for the qualitative detection of IgG antibodies against the nucleocapsid antigen against SARS-CoV-2 (Alinity System, Abbott Ireland Diagnostics Division, Ireland, RRID: AB_2924985), was performed from serum samples of patients with SARS-CoV-2 RT-PCR positivity who survived after COVID-19 infection. The manufacturer's recommended index value cutoff of 1.40 was used for IgG levels.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences Statistics software, version 25 (IBM SPSS Corp.; Armonk, NY, USA). Demographic and clinical data are expressed as mean ± SD, or if the data showed no normal distribution, as medians and ranges. Spearman and Pearson correlation tests were used to assess associations between variables. The chi-square test was used to compare nonparametric data, and the Student's *t*-test was used for the comparison of parametric variables. The paired sample *t*-test was used to show the difference between blood parameters before and during the COVID-19 infection. Logistic regression was performed to identify independent risk factors for death from the COVID-19 infection. Significance was defined at the 0.05 level.

MAIN POINTS

- The coronavirus disease 2019 (COVID-19) pandemic affected over 17 million people in Türkiye and hemodialysis patients were prone to infection with SARS-CoV-2 due to lack of isolation and decreased adaptive and innate immunity. Despite decreased immunity, our study showed that after SARS-CoV-2 infection, hemodialysis patients had a good antibody response after the disease.
- Although 79.1% had seroconversion, uncontrolled secondary hyperparathyroidism adversely affected the antibody response after COVID-19 infection.
- Attention should be paid to the treatment of hyperparathyroidism, especially during the pandemic period, and the need for early booster vaccination in some groups should be considered by monitoring antibodies.

RESULTS

Demographic and Clinical Characteristics of the Study Population

The study included 458 adult patients who received maintenance hemodialysis treatment for at least 6 months. The mean age of the study population was 60 ± 15 years. A total of 186 patients were female, and 272 patients were male. Hypertension and atherosclerotic heart disease were the most common comorbidities (50% and 42.4%), and diabetic nephropathy was the most common cause of kidney failure (21%). Sixty-two (13.5%) patients had a history of kidney transplantation. The mean dialysis vintage was 77 ± 69 months.

Severe Acute Respiratory Syndrome Coronavirus 2 Reverse Transcription Polymerase Chain Reaction Positivity in Maintenance Hemodialysis Patients

The COVID-19 infection was detected in 70 patients (15.3%) between March 2020 and February 2021, for whom a SARS-CoV-2 PCR test was performed after contact or having symptoms of infection. Ten patients (14.3%) were asymptomatic. Pulmonary involvement was present at admission in 3 asymptomatic patients (30%). Seroconversion was observed in 8 asymptomatic patients (80%).

Severe Acute Respiratory Syndrome Coronavirus 2 Immunoglobulin G Development After Coronavirus Disease 2019 Infection in Maintenance Hemodialysis Patients

The time from swab positivity to antibody testing was median 112 days (min 46-max 192 days). 20 patients died secondary to the COVID-19 infection, and 1 patient died due to a non-COVID-19 cause after infection, 1 patient was lost to follow-up, and antibody levels were measured in 48 patients. Seroconversion developed in 38 patients (79.1%) after an active infection. The COVID-19 infection develop again after 2 and 5 months from the first infection in 2 patients who did not developed seroconversion after the first infection. There was no difference in SARS-CoV-2 IgG titers between symptomatic or asymptomatic patients. The characteristics of hemodialysis patients with and without seroconversion are given in Table 1. Hematologic and biochemical parameters had no relationship with seroconversion status.

Antibody titers did not show a correlation with demographic features, COVID-19 symptoms, and comorbidities. Higher CRP levels during COVID-19 infection were associated with higher SARS-CoV-2 IgG titers (P = .014, r = .384). Remarkably, antibody levels were lower in patients with secondary hyperparathyroidism, regardless of blood calcium and phosphorus levels (Table 2). Adynamic bone disease [parathyroid hormone (PTH) < 150 ng/L] showed no effect on antibody development (P = .569). Calcium channel blocker use was associated with higher levels of SARS-CoV-2 IgG titers (3.60 ± 2.35 relative units (RU) vs. 5.96 ± 3.32 RU). While vitamin D use did not have an effect on the antibody response (P = .167), the antibody titer was lower in patients using cinacalcet (2.75 ± 1.43 RU vs. 4.79 ± 3.03 RU; P = .046). When linear regression analysis was performed with age, CRP during infection, calcium channel blocker use, and PTH values to find the factor that determines the COVID-19 IgG titer, it was shown that PTH was an independent variable in determining the COVID-19 IgG titer (P = .034; B = −.002; 95% CI = −0.004-0.00) (Table 3).

Mortality Related Factors After Coronavirus Disease 2019 Infection in Maintenance Hemodialysis Patients

Twenty of the 70 patients died of COVID-19 infection. The median time from swab positivity to death was 16 days (minimum 5 days–maximum 50 days). Comorbidities had no effect on COVID-19 mortality in maintenance hemodialysis patients (obesity P = .270, diabetes mellitus P = .324, hypertension P = .449, atherosclerotic heart disease P = .255, chronic obstructive pulmonary disease P = 1.000, history of kidney transplantation P = 1.000). Other factors associated with mortality are given in Table 4.

Table 1. Comparison of Hemodialysis Patients According to Their Seroconversion Status after COVID-19 Infection

	SARS-CoV-2 IgG Positive N = 38	SARS-CoV-2 IgG Negative N = 10	*P*
Age (years, mean ± SD)	60 ± 14	55 ± 17	.351
Gender (F/M, n)	16/22	3/7	.449
Dialysis vintage (months, mean ± SD)	84 ± 77	70 ± 55	.456
Socioeconomic status (n, %)*			
• Low	6 (15.7%)	3 (30%)	
• Medium	21 (55.2%)	6 (60%)	.364
• High Income	11 (28.9%)	1 (10%)	
Comorbidities			
• Obesity (BMI >35 kg/m^2, n, %)	6 (15.7%)	1 (10%)	.624
• Diabetes mellitus (n, %)	18 (47.3%)	3 (30%)	.293
• Hypertension (n, %)	20 (52.6%)	4 (40%)	.430
• AHD (n, %)	19 (50%)	5 (50%)	.940
• COPD (n, %)	8 (21%)	2 (20%)	.911
• History of Kidney Transplantation (n, %)	**2 (5.2%)**	**3 (30%)**	**.025**
Drug use (n, %)			
• ACEI/ARB	15 (39.4%)	2 (20%)	.230
• Calcium channel blocker	14 (36.8%)	2 (20%)	.362
• Diuretics	12 (31.5%)	2 (20%)	.446
• Acetylsalicylic acid	26 (68.5%)	5 (50%)	.230
• IV Iron	25 (65.7%)	7 (70%)	.761
• Vitamin D or analogs	30 (78.9%)	9 (90%)	.407
• Phosphate binder with Calcium	**36 (94.7%)**	**5 (50%)**	**<.01**
• Phosphate binder without Calcium	10 (35.7%)	5 (50%)	.151
• Cinacalcet	8 (21%)	3 (30%)	.549

AHD, atherosclerotic heart disease; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin 2 receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IV, intravenous; SARS CoV-2, severe acute respiratory syndrome coronavirus 2.
*The patients were divided into 2 groups according to SARS CoV 2-IgG results and compared using descriptive statistical methods.
**ANOVA analysis showed that COVID-19 infection was more frequent in patients with low income than in patients with medium income (P = .015).

Table 2. Correlation Analysis of Severe Acute Respiratory Syndrome Coronavirus 2 Immunoglobulin G Antibody Titers

SARS-CoV-2 Antibody titers	*P*	*r*
Creatinine	**.028**	**−0.320**
Calcium	.897	
Phosphorus	.549	
Albumin	.196	
Parathyroid hormone	**.009**	**−0.375**

SARS CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Factors Associated with Coronavirus Disease 2019 Immunoglobulin G Titer

	P	*B*	95% CI
Age	.845	0.001	−0.010-0.012
CRP	.099	0.014	−0.003-0.031
Calcium channel blocker use	.059	1.891	0.087-3.695
PTH	.034	−0.002	−0.004-0.00

CRP, C-reactive protein; PTH, parathyroid hormone.

Mortality was observed in patients who showed signs of more severe inflammation during the COVID-19 infection. In the regression analysis, when the white blood cell count, neutrophil count, CRP, N/L ratio, and lung involvement during infection were evaluated, it was observed that white blood cell count was an independent predictor of mortality (Table 5).

DISCUSSION

Our study showed that COVID-19 infection had a prevalence of 15.2% among hemodialysis patients in the early stages of the pandemic. Lung involvement and severity of inflammation was associated with COVID-19-associated mortality, and a high level of leukocyte count during infection was found to be an independent predictor of mortality. The remarkable point of our study is that antibody formation was suppressed in patients with secondary hyperparathyroidism.

Since the beginning of the pandemic, the frequency of COVID-19 infection has been reported between 5.5% and 19.8% among hemodialysis patients at different time intervals, and in our study, the prevalence was found to be 15.3%, as consistent with previous studies.[8] The increased prevalence of COVID-19 infection in hemodialysis patients compared to the normal population can be explained by the difficulty in maintaining social distance, dysfunction of the innate and adaptive immune systems associated with uremia, and existing multiple comorbidities.

In population studies, it has been observed that antibody positivity starts in 20 days and continues up to 1 year after COVID-19 infection, and the seroconversion rate is between 95 and 99% in people who have had the disease.[9,10] When hemodialysis cohorts were evaluated for seroconversion, rates ranging from 83% to 100% were reported.[11]

Table 4. Factors Associated with Mortality Due to Coronavirus Disease 2019 Infection

	Patients Died of COVID-19 infection, N = 20	Patients Recovered from COVID-19 Infection, N = 50	*P*
Age (years, mean ± SD)	66 ± 11	58 ± 15	.058
Gender (female/male, n)	8/12	20/30	1.0
Dialysis vintage (months, mean ± SD)	97 ± 93	85 ± 76	.369
Lung involvement (n, %)	**18 (90%)**	**27 (54%)**	**.01**
D-dimer (mg/L, median/minimum–maximum)*	2.70 (0.57-9.28)	1.29 (0.19-6.40)	.077
White blood bell count, baseline (/mm^3, mean ± SD)	7.2 ± 2.1	6.9 ± 2	.620
White blood cell count, during infection (/mm^3, median/minimum–maximum)	**7.84 (3.2-18.6)**	**4.8 (1.5-14.5)**	**.001**
Neutrophil count, baseline (/mm^3, mean ± SD)	4.9 ± 1.8	4.4 ± 1.6	.18
Neutrophil count, during infection (/mm^3, median/minimum–maximum)	**7.5** ± **4.6**	**4.2** ± **2.6**	**.001**
CRP level, baseline (mg/L, mean ± SD)	25 ± 5	23 ± 4	.725
CRP level during infection (mg/L, median/minimum–maximum)	109.5 (4.40-326.1)	45 (0.3-201)	.079
N/L ratio, baseline (/mm^3, median/minimum–maximum)	**3.20 (1.68-10.42)**	**2.54 (1.05-7.26)**	**.015**
N/L ratio, during infection (/mm^3, median/minimum–maximum)	**9.94 (1.84-102.6)**	**3.93 (0.86-24.42)**	**.013**

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; N/L, neutrophil/lymphocyte.
*Cutoff value for D-dimer is 0.44 mg/L.

Table 5. Logistic Regression Analysis of Coronavirus Disease 2019 Infection on Mortality in Hemodialysis Patients

	P	HR	95% CI
White blood cell count, during infection	.004	1.451	1.125-1.872
Lung involvement	.174		
CRP level during infection	.190		
Neutrophil count, during infection			

CRP, C-reactive protein; HR, hazard ratio.

Patients who do not develop SARS-CoV-2 IgG after infection usually have an asymptomatic infection, have an immunosuppressive condition, or are older.[11] Virus-specific T-cell response due to a viral infection is seen in 70% of the patients; even in the absence of antibody response, CD4+ T helper cells fight infection by secreting high-dose interferon gamma–.[12] Uremia-associated decrease in expression of costimulatory molecules in CD4+ T cells, low level of B cells, and impaired T-cell-dependent B-cell activity may explain the relatively low antibody response in hemodialysis patients. In our study, the presence of previous kidney transplantation adversely affected the development of antibodies.

The presence of hyperparathyroidism impairs the proliferation and function of B cells in chronic kidney disease.[13] Addition of high-dose parathyroid hormone to B cell culture or vaccination of rats with chronic kidney failure results in a decreased antibody response.[14,15] Another study shows that complement system elements—which play a key role in the development of humoral response—and immunoglobulin levels increase after parathyroidectomy in patients with chronic kidney failure.[16] High parathyroid hormone levels also impair T cell number and function.[6] These defects in immunity occur with increased cytosolic calcium levels and increased cAMP production in both B cells and polymorphonuclear leukocytes.[15,17]

Danthu et al showed a positive relationship between anti-Hbs and SARS-CoV-2 IgG.[18] Although we could not show statistical significance in our study, anti-Hbs titers were lower in patients who did not develop SARS-CoV-2 IgG. Hyperparathyroidism negatively affects the development of anti-Hbs after vaccination, and it may influence SARS-CoV-2 IgG development.[19] Use of vitamin D or analogs for treating secondary hyperparathyroidism reduces inflammation and oxidative stress, but in our study, no relationship was found between vitamin D or analog use and SARS-CoV-2 IgG levels.[20,21] In experimental studies, it has been observed that calcium channel blockers such as verapamil and nifedipine reduce the unfavorable effects of parathyroid hormone on the immune system by reducing the increased cytosolic calcium via calcium antagonistic effects.[17,21] Although blood calcium is lower in patients using calcium-containing phosphate binders, ionized calcium is high in the blood due to acidosis. Similarly, patients using phosphate binders without calcium have an elevated level of parathyroid hormone and blood calcium, which may affect the antibody response by increasing cytosolic calcium content. Secondary hyperparathyroidism may have influenced the antibody response rather than the calcium content of the phosphate binder that was used. According to these data, it is important to keep parathyroid hormone levels within the reference range recommended by the guidelines for appropriate antibody formation after an active viral infection like SARS-CoV-2.

Maintenance hemodialysis patients have 4-fold increased incidence for COVID-19 infection and 10-fold increased mortality when compared with the age-related population.[21,22] Previously, Neuen et al showed that the N/L ratio increases cardiovascular and all-cause mortality in hemodialysis patients.[23]

There are some limitations in our study. Serum samples of the patients for antibody measurement were not taken at the same time point after infection. SARS-CoV-2 IgG level was measured by anti-nucleocapsid antibody. Anti-nucleocapsid antibody rises earlier and wane in a shorter time after SARS-CoV-2 infection compared to anti-spike antibody.[24,25] In our study group, the antibody positivity was shown in approximately 80% of the patients, even 6 months after the infection. In the study by Cohen et al, antibodies were proven to be protective by reducing the risk of subsequent COVID-19 infection by 45% and clinically overt infection by 79% in patients who had SARS-CoV-2 and formed antibodies.[26] Although anti-spike antibodies are found to be more suitable for demonstrating seroconversion in the general population, especially in mild-to-moderate disease, our study has proven that anti-nucleocapsid antibodies can be used in the hemodialysis group.

In conclusion, bone and mineral metabolism play a substantial role in innate immunity to fight against SARS-CoV-2 infection in hemodialysis patients. Therefore, especially during pandemics, the treatment of secondary hyperparathyroidism is more substantial. Vaccination is prioritized in this immunocompromised patient group, and antibody status should be checked at intervals.

Ethics Committee Approval: This study was approved by Baskent University Institutional Review Board and Ethics Committee (Date: January 27, 2021; Number: 21/23).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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