

# Clinical features, management, and outcome of hemodialysis patients with SARS-CoV-2

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## Abstract

The aim of the study was to evaluate the clinical features of the patients on HD with COVID-19 and determine the prognostic factors. In this single-center prospective study, a total of 58 chronic renal failure patients on HD and diagnosed COVID-19 infection were enrolled in the study. The patients were divided into two groups according to their need for intensive care unit referral. Demographic features of the patients, clinical manifestations, laboratory data, treatments, and clinical outcome were evaluated. The mean age of 58 HD patients was  $63.2 \pm 13.8$  (30–93) years and female–male ratio was 0.34. SARS-CoV2-PCR positivity rate was 32.8%. 85.2% of patients ( $n = 46$ ) had bilateral lesions and 14.8% ( $n = 8$ ) had unilateral one lesion in chest CT. The most common symptoms were fatigue (in 44 patients, 80%) and dyspnea (in 31 patients, 56.4%). The most common comorbidity was HT (in 37 patients, 67.3%). The patients who need intensive care and died were older ( $p = 0.015$ ). We observed lower platelet and eosinophil counts, potassium levels, higher AST, troponin and CRP levels in the group of patients who need intensive care and died than the group who survived ( $p = 0.043, 0.005, 0.033, 0.007, 0.001, <0.001$ , respectively). 15.5% of the patients ( $n = 9$ ) were transferred to intensive care unit. Among them, two were discharged with cure and seven patients died. Mortality rate was 12.1%. Older age, lower platelet and eosinophil counts and higher AST, troponin and CRP levels were prognostic risk factors in our HD patients who needed intensive care.

## KEYWORDS

adult, COVID-19, hemodialysis, mortality, SARS-CoV-2

## 1 | INTRODUCTION

A new coronavirus outbreak severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019. On February 11, 2020, the World Health Organization officially changed the name of the disease caused by SARS-CoV-2 to *coronavirus disease*

2019 (COVID-19) [1]. It has spread to countries all over the world since December 2019. The first COVID-19 case was confirmed on March 10, 2020, and the World Health Organization declared a pandemic on March 11.

In addition to causing diffuse alveolar damage and acute respiratory failure, the virus enters the bloodstream

after lung infection and accumulates most frequently in the kidney and causes cell damage [1,2].

Epidemiological studies have shown that COVID-19 patients with comorbid diseases such as DM, hypertension (HT), cardiovascular diseases, or elder age are not only more susceptible to infection but also have more poor prognoses [3]. Uremia caused by chronic renal failure causes inflammation and immunosuppression at the molecular level [4]. Immunosuppression that occurs in chronic kidney failure can change the immune response to viral diseases [4]. These patients are vulnerable to respiratory pathogens and severe pneumonia due to the relative suppressed immunity and the frequent hospital admissions of these patients on dialysis [5].

Both the risk of pneumonia with chronic kidney diseases and the mortality rate due to pneumonia are 14 to 16 times higher than the general population [6]. However, to our knowledge, there are not enough scientific studies investigating the COVID-19 outbreak in patients with chronic kidney disease, especially HD patients.

In this prospective study, we aimed to determine whether the symptoms of patients on HD with COVID-19 are typical and whether they have different laboratory and radiologic abnormalities and clinical outcomes.

## 2 | MATERIALS AND METHODS

A total of 58 HD patients infected with SARS-CoV-2 were evaluated prospectively from March 11 to June 1, 2020, at the department of Infectious Diseases. HD patients with COVID-19 were divided into two groups according to intensive care need.

Demographic features of the patients, chronic diseases (DM, HT, chronic obstructive pulmonary disease, congestive heart failure, coronary vascular diseases, malignancy), symptoms at admission (fever, cough, dyspnea, diarrhea, vomiting, nausea, abdominal pain, muscle pain, conjunctivitis, loss of smell/taste), need for oxygen support in the follow-up (assessed by the presence of oxygen saturation in the room air <93%), need for intensive care, laboratory data (complete blood count, liver and kidney function test, biochemical tests, erythrocyte sedimentation rate, procalcitonin, CRP, coagulation parameters, electrocardiogram (ECG), treatments, and clinical outcome were evaluated.

Throat and nasopharyngeal swab samples for RT-PCR were collected from only those patients showing symptoms suggestive of the disease. The laboratory diagnosis of COVID-19 was implemented by the RT-PCR assay in accordance with the protocol established by the World Health Organization. After RNAs were extracted by a commercial kit (Bio-Speedy nucleic acid extraction kit, Bioeksen, Turkey), another commercial RT-PCR kit

(Bio-Speedy, COVID-19 RT-qPCR Kit, Bioeksen, Turkey) that targets RdRp gene of COVID-19 was used for detection of COVID-19 RNA in the samples [7].

Leukocytosis, neutrophilia, lymphopenia, and increased CRP were defined according to the given normal ranges of the hospital laboratory as follows: white blood cells >10 000  $\mu$ /L, leukocytosis; neutrophil count >7000  $\mu$ /L, neutrophilia; lymphocyte count  $\leq$ 800  $\mu$ /L, lymphopenia; platelets count <100 000  $\mu$ /L, thrombocytopenia and CRP >5 mg/L, increased CRP, respectively.

Diagnosis of COVID-19 pneumonia was based on the World Health Organization interim guidance [8] and the New Coronavirus Pneumonia Prevention and Control Program (fifth edition) published by the National Health Commission of China [9]. The patients were classified as mild, moderate, severe, and critical cases. Mild patients refer to patients with no radiographic evidence of pneumonia. Severe cases were defined as (i) respiratory rate >30 breaths/min, (ii) oxygen saturation  $\leq$ 93%, or (iii) PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $\leq$ 300 mm Hg. Critical severe cases were defined as including  $\geq$ 1 of the following criteria: shock; respiratory failure requiring mechanical ventilation; combination with other organ failures; and admission to intensive care unit [9].

All of the patients with symptoms suspected COVID-19 had CT. The findings such as ground glass opacities, consolidations, and cobblestone appearance were regarded typical for COVID-19. HD patients who had positive rRT-PCR for SARS-CoV-2 and/or typical findings of COVID-19 at chest CT were involved in this study.

The treatment protocol was as oseltamivir (30 mg 1  $\times$  1), hydroxychloroquine (2  $\times$  200 mg loading and 1  $\times$  200 mg maintenance dose), vitamin C (2  $\times$  15 g), and azithromycin (1  $\times$  500 mg loading and 1  $\times$  250 mg maintenance dose) for a total of 5 days as suggested by Ministry of Health's COVID-19. All of the patients were followed by ECG. Azithromycin and hydroxychloroquine therapy was discontinued if QTc >500 ms or QT >480 ms at the beginning or during the follow-up. Favipiravir therapy (2  $\times$  1600 mg loading and 2  $\times$  600 mg maintenance dose) was added to the patients who continued to have symptoms or developed clinical and/or laboratory decompensation after 5 days of hydroxychloroquine treatment.

The study protocol was approved by the local ethics committee (6 December, 2020, No: 2425). Written informed consents were taken from patients before treatment.

### 2.1 | Statistical analysis

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics; number and percentage

**TABLE 1** The demographic and clinical characteristics of the patients

Nationality	
Turkish Republic	52 (89.7%)
Others	6 (10.3%)
Sex	
Male	32 (55.2%)
Female	26 (44.8%)
Age (mean $\pm$ SD, years)	63.2 $\pm$ 13.8 (30–93)
Systolic blood pressure (mm Hg)	146.8 $\pm$ 29.1 (85–214)
Diastolic blood pressure (mm Hg)	76.4 $\pm$ 15.1 (50–111)
Chronic diseases	
Diabetes mellitus	21 (38.2%)
Hypertension	37 (67.3%)
Cardiovascular disease	24 (43.6%)
Tuberculosis	10 (18.2%)
Transplantation	1 (1.8%)
Chronic obstructive lung disease	9 (16.7%)
Malignancy	9 (16.7%)
Hepatitis B infection	1 (1.8%)
Hepatitis C infection	4 (7.3%)
Signs and symptoms	
Fever	23 (41.1%)
Fatigue	23 (41.8%)
Dyspnea	31 (56.4%)
Diarrhea	7 (12.7%)
Sore throat	8 (14.5%)
Myalgia	20 (36.4%)
Weakness	44 (80%)
Oxygen saturation rate (mean $\pm$ SD, %)	91.5 $\pm$ 5.0 (75–98)
Disease severity	
Mild	3 (5.6%)
Moderate	34 (63%)
Severe	15 (27.8%)
Very severe	2 (3.7%)
Complication rate	12 (21.8%)
Radiologic Findings	
Ground-glass opacity	20 (37%)
Cord shadow (consolidation)	21 (38.9%)
Patchy opacity	12 (22.2%)
Interstitial abnormalities	1 (1.9%)

(Continues)

**TABLE 1** (Continued)

Site of lung lesions	
Bilateral	46 (85.2%)
Unilateral	8 (14.8%)
PCR	
Positive	21 (36.2%)
Negative	37 (63.8%)

for categorical variables, mean, standard deviation, minimum, maximum, median for numerical variables. The comparisons of numerical variables in two independent groups were performed using Student *t*-test when normal distribution condition was met, and Mann–Whitney *U*-test when normal distribution condition was not met. The proportions in the groups were analyzed using the Chi-square test. Statistical significance level of alpha was accepted as  $p < 0.05$ .

This study was approved by the local institutional review board and waived the requirement for informed consent.

### 3 | RESULTS

Among 58 HD patients, 26 (44.8%) were female and 32 (55.2%) were male. The mean age was 63.2  $\pm$  13.8 (range: 30–93) years. Nineteen (32.8%) patients had positive rRT-PCR. All the patients had computerized tomography findings consistent with COVID-19 disease. 85.2% of patients ( $n = 46$ ) had bilateral lesions and 14.8% ( $n = 8$ ) had unilateral one lesion compatible with COVID-19 disease. The most common symptoms were fatigue (in 44 patients, 80%) and dyspnea (in 31 patients, 56.4%). There were no patients with abdominal pain, loss of smell/taste, and conjunctivitis. The most common comorbidities were HT (in 37 patients, 67.3%), congestive heart failure (in 24 patients, 43.6%), and DM (in 21 patients, 38.2%). The duration of follow-up was 1 month. The demographic and clinical characteristics of the patients are shown in Table 1.

When the demographical findings were compared, the only significant factor was age for need for the admission to the intensive care unit. The patients transferred to the intensive care unit were older compared to the others ( $p = 0.015$ ) (Table 2).

The mean white blood cell count was 8431.6  $\pm$  4753.3. The mean lymphocyte count was 1206.7  $\pm$  1434.4. The mean platelet count was 231.5  $\pm$  88.7. All patients had high CRP values and normal procalcitonin levels (Table 3).

We observed lower platelet and eosinophil counts and potassium level and higher AST, troponin and CRP levels

TABLE 2 The characteristics of the patient groups according to prognosis

	Discharge ( <i>n</i> = 46)	Intensive care unit-Exitus ( <i>n</i> = 9)	<i>p</i>
Nationality			
Turkish Republic	43 (87.8%)	9 (100%)	0.576
Others	6 (12.2)	0	
Sex			
Male	25 (51%)	7 (77.8%)	0.167
Female	24 (49%)	2 (22.2%)	
Age (mean ± SD, years)	61.3 ± 12.9	73.3 ± 14.9	0.015
Systolic blood pressure (mm Hg)	148.8 ± 29.6	135.4 ± 24.1	0.207
Diastolic blood pressure (mm Hg)	76.6 ± 15.6	75.2 ± 12.5	0.966
Chronic diseases			
Diabetes mellitus	18 (39.1%)	3 (33.3%)	1.000
Hypertension	31 (67.4%)	6 (66.7)	1.000
Cardiovascular disease	18 (39.1%)	6 (66.7%)	0.157
Tuberculosis	9 (19.6%)	1 (11.1%)	1.000
Transplantation	0	1 (11.1%)	0.164
Chronic obstructive lung disease	7 (15.6%)	2 (22.2%)	0.635
Malignancy	7 (15.6%)	2 (22.2)	0.635
Hepatitis B infection	1 (2.2%)	0	1.000
Hepatitis C infection	4 (8.7%)	0	1.000

Note: *p* < 0.05 is statistically significant.

Abbreviation: SD, standard deviation.

in the group of patients who need intensive care and died than the group who survived (*p* = 0.043, 0.005, 0.033, 0.007, 0.001, <0.001, respectively). No significant differences were detected in other laboratory parameters between groups.

The patients who had abnormal ECG (QTc > 500 ms) findings did not receive hydroxychloroquine and azithromycin treatment. There has not been any need for treatment discontinuation due to ECG changes associated with azithromycin or hydroxychloroquine treatments. Twenty patients received favipiravir treatment alone or combination with other treatment (Table 4). There was significant difference in antiviral treatment between the patients who need intensive care and discharged patients (*p* = 0.004). Favipiravir was initiated in all of the patients who need intensive care. All of the patients in intensive care unit had received antibacterial treatment (moxifloxacin, carbapenem, vs) for secondary bacterial infection.

The mean oxygen saturation of the patients was 91.5 ± 5.0 (75–98) at admittance. In the follow-up, 15.5% of the patients (*n* = 9) who had moderate acute respiratory distress syndrome (ARDS) (100 < PaO<sub>2</sub>/FIO<sub>2</sub> ≤ 200, PEEP ≥ 5 cm H<sub>2</sub>O) transferred to intensive care unit and received invasive ventilation. Among them, two were

discharged with cure and seven patients died whereas all of the patients who did not required intensive care were discharged with cure (Table 5). The mean median time from diagnosis to death was 19.57 ± 17.23 (median 5–59 days) days.

## 4 | DISCUSSION

The mortality rate of novel coronavirus disease has been estimated approximately 2%, which is lower than severe acute respiratory syndrome (SARS; mortality rate, >40% in patients aged >60 years) and the Middle East respiratory syndrome (MERS; mortality rate, 30%) [10]. There is limited number of studies examining COVID-19 infection in HD patients.

HD patients have a proinflammatory state with functional defects in innate and adaptive immune cell populations and are known to have a higher risk for upper respiratory tract infection and pneumonia [1,11]. The other proposed pathogenetic mechanisms were the uremia-related impairment in monocyte, neutrophil phagocytosis [12], T lymphocytes [13], B lymphocytes [14], and increased cytokines [15]. Su et al. [2] studied 26 autopsies of infected patients with SARS-CoV-2 and

TABLE 3 The laboratory findings of the patients

	Mean, SD	Max-min
Hemoglobin (g/dl)	10.3 ± 2.4	5–17
Platelet count ( $\times 10^9/L$ )	231.5 ± 88.7	89–515
White blood cell count	8431.6 ± 4753.3	10.2–26 100
Lymphocyte count	1206.7 ± 1434.4	80–8850
Neutrophil count	6654.1 ± 3764.4	1010–23 650
Eosinophil count	71.7 ± 173.0	0–830
Albumin (g/dl)	36.9 ± 7.7	3.7–51
Urea (mg/dl)	134.9 ± 63.2	44–329
Creatinine (mg/dl)	6.4 ± 2.8	2.2–14.47
Serum sodium	134.9 ± 5.4	114–144
Serum potassium (meq/L)	4.8 ± 1.1	2.7–9.5
Uric acid (mg/dl)	6.9 ± 4.3	1.5–23
Creatine kinase (IU/L)	99.8 ± 207.1	9–1502
Lactic dehydrogenase (IU/L)	301.6 ± 206	121–1335
Alanine aminotransferase (IU/L)	14.7 ± 13.3	3–78
Aspartate aminotransferase (IU/L)	22.1 ± 16.1	5–84
Blood glucose (mg/dl)	130.8 ± 47.5	60–282
C-reactive protein (mg/L)	100.5 ± 93.9	0.8–323
Ferritin ( $\mu\text{g/L}$ )	684.9 ± 515.7	51–1500
Serum calcium (mg/dl)	8.7 ± 0.9	6.5–11.7
Serum phosphate (mg/dl)	5.03 ± 7.19	0.30–34
D-dimer (mg/L)	5.0 ± 7.2	0.3–34
Fibrinogen (g/L)	462.3 ± 157.8	5–775
Procalcitonin (ng/ml)	10.8 ± 26.3	0.05–98
Troponin I (g/ml)	119.6 ± 256.1	4.9–1204

Note:  $p < 0.05$  is statistically significant.

showed direct evidence of the invasion of SARS-CoV-2 in the kidney tissue.

HD patients were underwent daytime conventional HD 4 h/day (blood flow rate standard 300 ml/min and dialysate flow rate Standard 500 ml/min) in this study.

The mean age of our patients was  $63.2 \pm 13.8$  years, similar with the other reports [6,16,17] indicating that HD patients infected with COVID-19 are older patients. The most common symptoms were dyspnea, and fatigue in our study. In the other studies, dyspnea, fever, and cough were the most common symptoms in both HD and non-HD patients [4,16,18]. The incidence of fever in our patients is not as high as that of the general population [3,19]. The most common comorbid disease was HT in our both group, compatible with the literature [4,16,20].

TABLE 4 Treatment modalities in patients

Antiviral treatment	
None	29 (50%)
Oseltamivir	8 (13.7%)
Favipiravir	16 (27.5%)
Favipiravir + oseltamivir	5 (8.6%)
Fluid replacement	2 (3.7%)
Antibiotics	39 (72.2%)
Corticosteroids	4 (7.4%)
Hydroxychloroquine	58 (100%)
Azithromycin	41 (74.5%)
Anticoagulation	47 (85.5%)
Mechanical ventilation	
Invasive	8 (14.5%)
Non-invasive	47 (85.5%)

TABLE 5 Outcome of the patients

Discharge	49 (84.5%)
Intensive care unit	2 (3.4%)
Exitus	7 (12.1%)

During the first month of the pandemic, all patients with suspected symptoms of COVID-19 had undergone CT imaging driven diagnoses, due to PCR tests resulting within 48 to 72 h, in order to make a faster diagnosis and early management of the cases in our country. Therefore, all of our patients had findings in CT.

Severe COVID-19 disease, need for intensive care, and mortality were associated with leukocytosis, lymphopenia, neutrophil elevation, thrombocytopenia, and elevated CRP in general population. In laboratory examinations, all of the patients in both groups had high CRP levels. Shang et al. [21] reported that CRP, neutrophil count, LDH, white blood cell count, albumin, and procalcitonin were predictive on the prognosis of HD patients with COVID-19 and CRP was the strongest single predictive laboratory indicator. Higher CRP level has been associated with unfavorable aspects of COVID-19 diseases, such as cardiac injury, and ARDS development, and fatality [22,23]. In our study, we observed lower platelet and eosinophil counts and potassium level and higher AST, troponin and CRP levels in the group of patients who need intensive care and died than the group who survived ( $p = 0.043, 0.005, 0.033, 0.007, 0.001, <0.001$ , respectively). Thus, the detection of CRP levels in COVID-19 with HD patients is important in assessing the severity of disease.

Although low albumin and high LDH suggested poor prognosis in HD patients with COVID-19, as well as COVID-19 patients without HD [21], we did not observe significant difference in levels of albumin and LDH in our patients. Lymphopenia was reported to be a predictor of prognosis in COVID-19 patients [4,24]. However, our study showed no association between lymphopenia and prognosis of COVID-19 in HD patients, in similar with the study conducted by Shang et al. [21].

Zou et al. [19] has reported that fever, dyspnea, and elevated D-dimer levels were the poor prognostic factors in HD patients and important in determining severe disease at an early stage of COVID-19 infection and intensive care requirement. Some researchers also have determined higher white blood cell count, longer PT time, and higher D-dimer level as poor prognostic factors in HD patients with COVID-19 [25], but we did not find significant association between D-dimer levels, PT time, white blood cell count, and disease severity.

One of the largest studies conducted in HD patients has reported overall mortality rate as 29% [17]. Our mortality rate was 12.1%. Early diagnosis, hospitalization, and treatment had been conducted after symptom onset. Optimal supportive care to maintain proper oxygenation and vital signs, early administration of antiviral agents, could contribute to favorable outcomes.

The limitations of this study are small sample size from single center, observation time is too short to study the long-term damage and prognosis of HD patients, lack of extracorporeal membran oxygenation (ECMO), and unavailability of testing possible atypical pneumonia pathogens. Only univariate analysis was performed and the results of multivariate analysis were not presented due to small number of patients.

Although preventive measures such as education of medical staff and HD patients, increasing the social distance between the patients, strengthening the disinfection of dialysis rooms, early testing of possible suspected patients with COVID-19, separating the patients with symptoms and COVID-19 infection from non-infected HD patients, 58 HD patients were infected with COVID-19 and 15.5% of our HD patient needed intensive care unit.

In conclusion, HD patients have impaired immunity, thus early detection and diagnosis of COVID-19 infection, early isolation, and management are mandatory for preventing need for intensive care and reducing mortality of HD patients with COVID-19.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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