

Management of COVID-19 in 55 hemodialysis patients: Experience from Eastern Turkey

COVID 19 and hemodialysis

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Abstract

Aim: The novel coronavirus causes acute severe respiratory syndrome (SARS COV 2), and the disease is named COVID-19. The virus spreads easily, and COVID-19 may be asymptomatic or cause severe pneumonia and ARDS. Hemodialysis patients are affected by COVID-19 because of the immunosuppression caused by uremia, comorbid diseases and the risk of cross-contamination during dialysis. In this study, we aimed to examine the clinical features and outcomes of 55 hemodialysis patients diagnosed with COVID-19.

Material and Methods: Fifty-five hemodialysis patients who met the COVID-19 probable case definition were included in the study. Clinical and laboratory features were recorded from patient files and electronic data retrospectively.

Results: The study included 55 patients, the average age was 59.6 ± 13.2 years, 49% (n = 27) were female. Hypertension, Diabetes Mellitus, coronary heart diseases were the most common comorbid diseases. Comparing survivors and non-survivors, it was seen that the non-survivors were older (p=0.010). Logistic regression analyses revealed that age, SO₂, lactate, WBC, neutrophil count, CRP, LDH, CK, ALT, AST, albumin, total protein, ferritin and D-Dimer were associated with the risk of mortality.

Discussion: Myalgia, cough, and shortness of breath are the most common symptoms of COVID-19 infection in HD patients, with no apparent fever. Age, SO₂, WBC count, neutrophil count, CRP, LDH, CK, ALT, AST, albumin, total protein, ferritin and D-Dimer were found to be associated with mortality. Close monitoring of these parameters during the follow-up and treatment of patients may provide additional benefits in terms of survival.

Keywords

COVID 19; Hemodialysis; Mortality

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Introduction

A new type of coronavirus that emerged in Wuhan, People's Republic of China in December 2019 causes acute severe respiratory syndrome (SARS COV 2), and the disease is named COVID-19 (Corona Virus Disease 19) [1]. The virus spread all over the world in a short time and was declared a pandemic by the World Health Organization on March 11, 2020. The first case of the disease in our country was reported on March 10, 2020. The pandemic has put a heavy burden on health systems and country economies, as there is no effective treatment and vaccine available yet.

The virus is transmitted from person to person by airborne droplets and by direct contact, and the incubation period varies between 2-14 days (average 5 days). Respiratory symptoms such as fever, cough and shortness of breath are common symptoms of the disease COVID-19 may be asymptomatic or cause severe pneumonia and acute respiratory distress syndrome (ARDS). Although some comorbid conditions have been identified, such as old age and chronic disease, the course of the disease and what clinical symptoms may occur in which patient is not yet known.

Immune dysfunction caused by chronic uremia is present in patients with end-stage renal disease (ESRD) who are on hemodialysis (HD); therefore, these patients are more likely to have infections. In addition, comorbid conditions such as diabetes, cardiovascular disease and hypertension are more common in hemodialysis patients. These patients who are generally older, regularly visit the hospital or dialysis center and stay in the same indoor environment with other patients and staff for 3-4 hours each session, which increases cross-contamination [2]. There are studies examining the course of the disease, the response to available treatments, and mortality in hemodialysis patients, but the disease is still full of uncertainties [3, 4]. Therefore, in this study, we aimed to examine the clinical features and outcomes of 55 hemodialysis patients diagnosed with COVID-19.

Material and Methods

Fifty-five hemodialysis patients who met the COVID-19 probable case definition were included in the study. All patients were treated at the pandemic hospital in our region between March 22 and September 1, 2020.

Our study was designed as a retrospective cross-sectional study. The demographic characteristics (such as age, gender) of the patients included in the study, chronic diseases, complaints during hospitalization, pH, oxygen saturation (SO₂), lactate, bicarbonate (HCO₃), white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count (10⁹/L), hemoglobin (g/dL), alanine aminotransferase (ALT) (U / L), aspartate aminotransferase (AST) (U/L), Total Bilirubin (mg / dL), Lactate Dehydrogenase (LDH) (U / L), Creatinine Kinase CK (U / L), Blood Urea Nitrogen (BUN) (mg / dL), Creatinine (mg / dL), Albumin (mg / dL), D-dimer (ng / mL), Biomarker values such as ferritin (ng / mL), C-reactive protein (CRP) (mg / L) and Procalcitonin (PCT (ng/mL), whether there was admission to the ICU during follow-up, the treatments given, survival were recorded from patient files and electronic data retrospectively. CT images and reports of the patients were accessed from the hospital's

information system. The study was conducted with the necessary permissions from the Erzurum Regional Training and Research Hospital Ethics Committee and the Turkish Ministry of Health.

Statistical analysis

All procedures were performed using IBM SPSS Statistics 22.0 software. The results are presented as mean ± standard deviation (SD). Pearson's chi-square and Fisher's exact test were used for categorical variables where appropriate. After checking the normality distribution of scale variables using the Shapiro-Wilk test, independent samples were compared with appropriate significance tests (e.g., the Mann-Whitney U test, Kruskal-Wallis H test). When comparing more than two independent variables, the Bonferroni correction was applied post-hoc (Mann-Whitney U test and z-test) after the Kruskal-Wallis H test and Pearson's chi-square test. We also performed a univariate logistic regression for mortality (dependent), establishing predicting factors such as age, various laboratory parameters (independent variables), and their odds ratios (OR). Two-sided p-values of < 0.05 were considered statistically significant.

Results

Fifty-five hemodialysis patients diagnosed with COVID-19 were included in our study. The average age of the patients was 59.6 ± 13.2 (min: 31, max: 87) years, 49% (n = 27) were females, 51% (n = 28) were males, and dialysis duration was 59.9 ± 41.1 (2-237) months. The most common complaint of the patients was myalgia with 70.9%. This was followed by cough with 67.3%, shortness of breath with 58.2% and fever with 40%. The most common comorbid diseases in patients were hypertension (96.4%), diabetes mellitus (74.5%), coronary artery disease (47.3%) and heart failure (20%). While findings of COVID-19 were detected on CT in 44 patients, CT was normal in 7 patients. CT could not be performed in 4 patients due to technical reasons; 87.2% of the patients received favipiravir, 32.7% hydroxychloroquine, 76.4% low molecular weight heparin (LMWH), and 52.7% corticosteroid treatment. Immune plasma was given to 2 patients and tocilizumab treatment was administered to 2 patients. While 14 (25.5%) patients needed intensive care during follow-up, 12 (21.8%) patients died.

Comparing patients with and without intensive care need, it was observed that the mean age of the patients followed up in the intensive care unit was higher, all patients developed covid pneumonia on tomography, and the mortality rate was higher (p = 0.001, p = 0.032, p = 0.000, respectively). In addition, while the oxygen saturation and serum albumin levels of the patients followed up in the intensive care unit were statistically significantly lower, WBC, neutrophil, CRP, procalcitonin, LDH, AST, ferritin, D-Dimer, INR values were higher (p = 0.006, p = 0.010, p = 0.000 p = 0.000, p = 0.001, p = 0.009, p = 0.004 p = 0.029, p = 0.021, p = 0.023, p = 0.003, respectively), shortness of breath and myalgia symptoms were found to be more frequent. (p = 0.002, p = 0.022). The data are shown in Table 1. Comparing survivors and non-survivors, it was seen that the non-survivors were older (p = 0.010). Coronary heart disease was the most common chronic disease among non-survivors (p = 0.025). The symptom that was statistically significant in

the non-survivor group was shortness of breath (p = 0.001). The lactate, WBC, neutrophil, MPV, CRP, procalcitonin, LDH, CK, ALT, AST, ferritin, D-Dimer, INR values of the non-survivors were found to be statistically significantly higher (p = 0.00, p <0.001, p <0.001, p = 0.002, p = 0.007, p = 0.001, p = 0.001, p = 0.008, p = 0.029, p <0.001, p = 0.016, p = 0.003, p = 0.041, respectively). Oxygen saturation and albumin levels of these patients were found to be statistically significantly lower (p <0.001, p = 0.007). These data are given in Table 2.

Table 1. Comparison of patients according to follow-up

	Outpatient (n=12)	Service (n=29)	ICU (n=14)	p
Gender (F/M)	6/6	15/14	6/8	0,860
Age (year)	66 ± 10,1	53,6 ± 12,4	66,5 ± 11,8	0,001^{a,c}
Dialysis Duration (Month)	56,6 ± 33	65,9 ± 47,4	50,4 ± 32,7	0,572
PCR +/-	12/0	25/4	11/3	NA
CT finding +/-	7/2	23/5	14/0	NA
Comorbidity				
HT	11/1	29/0	13/1	NA
DM	8/4	9/29	9/5	0,039
CHD	8/4	20/9	13/1	NA
COPD	4/8	3/26	4/10	NA
CD ≥2	9/3	22/7	14/0	NA
CD ≥3	6/6	13/16	10/4	0,256
pH	7,318 ± 0,13	7,355 ± 0,07	7,352 ± 0,12	0,934
SO ₂ (%)	91,7 ± 5,6	91,2 ± 5,7	82,6 ± 9,5	0,006^{a,c}
Lactate (mmol/L)	4,2 ± 6,3	1,86 ± 0,73	2,7 ± 1,7	0,461
HCO ₃ (mEq/L)	19,5 ± 5,8	21,3 ± 3,4	20,2 ± 4,5	0,651
WBC (10 ³ /μL)	6538,2 ± 2783,4	4815,2 ± 2190,8	9329,3 ± 4492	0,000^{b,c}
Neutrophil (10 ³ /μL)	4761,9 ± 2747,6	3121,3 ± 1531,7	8130,7 ± 4128,1	0,000^{b,c}
Lymphocyte (10 ³ /μL)	1127,5 ± 614	926,2 ± 624,8	683,6 ± 280,1	0,097
Hemoglobin (gr/dL)	11,9 ± 1,9	10,9 ± 2,2	10,9 ± 2,3	0,389
Platelets (10 ³ /μL)	165.181,8 ± 73.56,3	172.586,2 ± 53.277,3	185.214,3 ± 56.877,9	0,394
CRP (mg/L)	33,4 ± 177,6	58,5 ± 50,7	148,1 ± 107,3	0,001^{a,c}
Procalcitonin (ng/mL)	-	0,86 ± 0,67	16,55 ± 31,9	0,009^{b,c}
LDH (U/L)	327,3 ± 177,6	316,6 ± 129,2	624,9 ± 570,5	0,004^{a,c}
CK (U/L)	105,9 ± 80,9	170,2 ± 252,6	417,8 ± 541,5	0,109
ALT (U/L)	29,1 ± 27,7	25,4 ± 19,2	56,1 ± 68,9	0,366
AST (U/L)	65,2 ± 139,4	31 ± 30,6	71,3 ± 69,9	0,029^{b,c}
Albumin (g/L)	34,5 ± 6,5	36,5 ± 4,8	32,5 ± 3,5	0,010^{b,c}
Ferritin (ng/mL)	933,9 ± 643,6	1024,8 ± 625,6	2389,1 ± 2230,7	0,021^{b,c}
D-Dimer (ng/mL)	1,86 ± 1,6	6,91 ± 9,24	7,83 ± 10,4	0,023^{b,c}
INR	1,33 ± 0,08	1,09 ± 0,19	1,74 ± 1,54	0,003^{a,c}
Uric acid (mg/dL)	5,4 1,3	5,1 1,8	6,3 2,2	0,272
Symptoms				
Fever	3/9	14/15	5/9	0,357
Shortness of breath	3/9	16/13	13/1	0,002^{a,c}
Cough	7/5	22/7	8/6	NA
Myalgia	10/2	16/13	13/1	NA
Headache	5/7	6/23	3/11	NA
Diarrhea	0/12	4/25	1/13	NA

ICU: Intensive Care Unit, HT: Hypertension, DM: Diabetes Mellitus, CHD: Coronary Heart Disease, COPD: Chronic obstructive pulmonary disease, CD: Comorbid Diseases, SO₂: Oxygen saturation, WBC: White Blood Cells, CRP: C-reactive Protein, LDH: Lactate Dehydrogenase, CK: Creatine Kinase, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, INR: Internationalized Normalized Ratio

^a: p < 0.05 for the difference between the outpatient and service groups;

^b: p < 0.05 for the difference between the outpatient and ICU groups;

^c: p < 0.05 for the difference between the service and ICU groups

The Kruskal–Wallis H with the Mann–Whitney U test, and Pearson’s chi-square test with the z-test were used. Bonferroni correction was applied as post-hoc after the Kruskal–Wallis H and chi-square tests. Significant values are shown in bold.

Logistic regression analyses were performed to identify the association of various factors with p-values < 0.05, such as age, SO₂, lactate, WBC, neutrophil count, CRP, LDH, CK, ALT, AST, albumin, total protein, ferritin and D-Dimer with the risk of mortality. The odds ratios and significance levels of univariate analyses are shown in Table 3.

Table 2. Comparison of survivors and non-survivors

	Non-Survivors (n=12)	Survivors (n=43)	p
Gender (F/M)	4/8	23/20	0,329
Age (year)	68,3 ± 11,1	57,2 ± 12,9	0,010
Dialysis Duration (Month)	64,4 ± 32,4	58,7 ± 43,5	0,445
Duration of Hospitalization (days)	11,4 ± 9,5	7,3 ± 7,5	0,166
PCR +/-	10/2	38/5	0,639
CT finding +/-	12/0	32/7	0,177
Comorbidity			
HT	11/1	42/1	0,385
DM	7/5	19/24	0,517
CHD	12/0	29/14	0,025
COPD	3/9	8/35	0,689
CD ≥2	12/0	33/10	0,108
CD ≥3	9/3	20/23	0,096
pH	7,294 ± 0,14	7,362 ± 0,06	0,133
SO ₂ (%)	80,3 ± 8,9	91,6 ± 5,3	< 0,001
Lactate (mmol/L)	4,2 ± 4,4	1,8 ± 0,7	0,005
HCO ₃ (mEq/L)	18,8 ± 5,3	21,5 ± 3,3	0,049
WBC (10 ³ /μL)	9762,5 ± 4648,7	5357,6 ± 2461,1	< 0,001
Neutrophil (10 ³ /μL)	8565,8 ± 4241,4	3665,2 ± 2081,3	< 0,001
Lymphocyte (10 ³ /μL)	718,3 ± 281,8	957,4 ± 616	0,190
Hemoglobin (gr/dL)	11,9 ± 2,4	10,9 ± 2	0,274
Platelets (10 ³ /μL)	179.833,3 ± 56.320,2	172.785,7 ± 59.049,6	0,553
CRP (mg/L)	136 ± 99,4	60,9 ± 64,4	0,007
Procalcitonin (ng/mL)	20,9 ± 35	0,84 ± 0,6	0,001
LDH (U/L)	691,6 ± 604,5	314,7 ± 122,9	0,001
CK (U/L)	483,1 ± 562,3	146,9 ± 215,9	0,008
ALT (U/L)	68,4 ± 72	24,3 ± 18,3	0,029
AST (U/L)	116,3 ± 129,1	28,2 ± 26,5	< 0,001
Albumin (g/L)	31,7 ± 4,7	36 ± 4,9	0,007
Ferritin (ng/mL)	2469,4 ± 2376,4	1056,2 ± 687,6	0,016
D-Dimer (ng/mL)	9,58 ± 12,1	2,52 ± 2,4	0,003
INR	1,89 ± 1,7	1,1 ± 0,2	0,041
Uric Acid (mg/dL)	6,5 ± 2,4	5,2 ± 1,6	0,059
Symptoms			
Fever	4/8	18/25	0,744
Shortness of breath	12/0	20/23	0,001
Cough	8/4	29/14	1,000
Myalgia	11/1	28/15	0,147
Headache	3/9	11/32	1,000
Diarrhea	1/11	4/39	1,000

HT: Hypertension, DM: Diabetes Mellitus, CHD: Coronary Heart Disease, COPD: Chronic obstructive pulmonary disease, CD: Comorbid Diseases, SO₂: Oxygen saturation, WBC: White Blood Cells, CRP: C-reactive Protein, LDH: Lactate Dehydrogenase, CK: Creatine Kinase, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, INR: Internationalized Normalized Ratio
Mann–Whitney U test and Pearson’s chi-square, and Fisher’s exact tests was used
Significant values are shown in bold.

Table 3. Evaluation of factors associated with mortality by univariate logistic regression analysis

	β i	Odds Ratio	%95 C.I.		Wald value	p value
Age (year)	0,074	1,077	1,014	1,144	5,836	0,016
SO ₂ (%)	-0,197	0,821	0,738	0,914	13,088	< 0,001
Laktat (mmol/L)	1,104	3,016	1,184	7,684	5,355	0,021
WBC (10 ³ /μL)	< 0,001	1,000	1,000	1,001	8,998	0,003
Neutrophil (10 ³ /μL)	0,001	1,001	1,000	1,001	10,855	0,001
CRP (mg/L)	0,011	1,011	1,002	1,020	6,190	0,013
LDH (U/L)	0,007	1,007	1,002	1,012	8,511	0,004
CK (U/L)	0,003	1,003	1,000	1,006	4,482	0,034
ALT (U/L)	0,032	1,007	1,059	1,032	6,216	0,013
AST (U/L)	0,032	1,032	1,005	1,060	5,597	0,018
Albumin (g/L)	-0,164	0,848	0,742	0,970	5,815	0,016
Total Protein (g/L)	-0,146	0,864	0,777	0,962	7,155	0,007
Ferritin (ng/mL)	0,001	1,001	1,000	1,002	3,730	0,053
D-Dimer (ng/mL)	0,163	1,177	1,000	1,385	3,842	0,050

β i = regression coefficient, CI = confidence interval
Significant values are shown in bold

Discussion

Infection risk is increased in chronic kidney disease (CKD), and infections are the second leading cause of death after cardiovascular disease. The increased risk of infection is more marked, especially in hemodialysis patients. COVID-19 infection, which started in China in December 2019 and turned into a pandemic in a short time, affects older individuals with serious chronic diseases (such as cardiovascular disease, diabetes, chronic kidney disease, chronic lung diseases, chronic liver disease, cancer) more [5]. Hemodialysis patients have a high risk of COVID-19 infection due to both CKD itself and their existing comorbidities [6]. Therefore, studies are needed to demonstrate the clinical characteristics and outcomes of COVID-19 infection in HD patients. Our study, which examined 55 HD patients with COVID-19 infection, is one of the studies with the largest number of patients in the literature.

The average age of 55 patients included in the study was 59.6 ± 13.2 (min: 31, max: 87) years, 49% (n = 27) were females, 51% (n = 28) were males. The fact that the number of female and male patients is similar differs from the fact that the number of male and female patients is more dominant in the general population [7]. The reason why COVID-19 infection is less common in women is thought to be a positive effect of the X chromosome and sex hormones on the natural and acquired immune system [8]. However, changes in sex hormones in women with end-stage renal disease may cause significant differences compared with the general population [9]. We think that the lack of gender difference in our patient group is due to the negative effect of chronic uremia on the immune system in HD patients.

The most common symptoms in COVID-19 infection are fever, myalgia, cough and shortness of breath [10, 11]. While gastrointestinal symptoms were common in a study of HD patients, a small number of patients in our group had gastrointestinal symptoms such as diarrhea, nausea and vomiting [12]. In our study, the most common symptoms were myalgia, cough, and shortness of breath. Unlike studies

conducted in the general population, fever is not a common symptom in our patient group. In our study, the most common comorbid diseases in HD patients are HT, CHD and DM. This finding is consistent with studies in HD patients and the general population [13, 14].

PCR was found to be positive in 48 of 55 patients included in the study and COVID pneumonia was observed in 86% of 51 patients who underwent CT. There was no clinically significant difference in the comparison of PCR positive and negative patients. INR value and the need for ICU were significantly higher in patients with lung involvement. Pulmonary involvement was observed more frequently in patients with 3 or more comorbid diseases. Both PCR and CT positivity did not make a significant difference in terms of mortality. Among the patients, 21.8% were followed at home, and 25.5% needed an ICU. It was found that the mean age and mortality rates of the patients who needed ICU were significantly higher, and all patients had pulmonary involvement. The albumin levels and oxygen saturations of the patients who needed ICU were lower. WBC, CRP, procalcitonin, LDH, AST, ferritin, D-Dimer and INR levels were found to be significantly higher. Studies have also found that age and D-Dimer levels are higher in patients who need ICU [15, 16].

Since HD patients have comorbid diseases and are more susceptible to infection, mortality from COVID-19 infection is considerably higher than in the general population [17]. Similarly, in our study, 21.9% of our patients died due to COVID-19 infection and related complications. Those with severe COVID-19 infection have been shown to have lower leukocyte, platelet, lymphocyte count and higher D-dimer, total bilirubin, troponin, LDH, AST, creatinine, PCT, ferritin and CRP levels than those without COVID-19 [18, 19]. In studies conducted with HD patients, the situation is a little more complicated. In the studies performed, generally, no significant relationship was found between leukocyte, neutrophil and lymphocyte counts and mortality [3, 4]. In our study, it was found that the WBC and neutrophil counts at the time of admission were significantly higher in non-survivors. In the regression analysis, both WBC and neutrophil count were found to be associated with mortality. Inflammation and inflammatory storm during viral infections cause systemic inflammatory damage. Some markers such as CRP, PCT, D-Dimer, ferritin and INR are frequently used in clinical practice as indicators of this inflammation. Although CRP is widely used in HD patients, the use of PCT is still controversial. Studies have emphasized that the PCT level is associated with the CKD stage and that the serum range for PCT should be a little wider in HD patients [20, 21]. In our study, CRP, PCT, INR, ferritin and D-Dimer levels were found to be significantly higher in both patients who died and those who needed ICU follow-up. Another remarkable point of our study is that this increase in CRP, ferritin and D-dimer levels was associated with mortality. In our patient group, whose albumin value, which is used in daily practice as a negative acute phase reactant, was found to be significantly lower, it was found to be associated with mortality. Muscle damage and myalgia, which often occur with viral infection, are directly related to the damage of muscle fibers by direct virus effect and, more likely, by myotoxic cytokines that occur in virus infections, especially tumor necrosis factor

(TNF). This situation causes an increase in the serum levels of intracellular enzymes such as CK and AST. High CK levels has been associated with a poor prognosis in some viral infections [22-24]. While there was no significant difference in CK, AST, LDH and ALT in COVID-19 studies conducted in HD patients, in our study, these four parameters were found to be significantly higher among non-survivors [3, 17]. In addition, these four parameters were associated with mortality.

As a result, while myalgia, cough and shortness of breath are the most common symptoms of COVID-19 infection in HD patients, the presence of fever is not evident. Age, SO₂, WBC count, neutrophil count, CRP, LDH, CK, ALT, AST, albumin, total protein, ferritin and D-Dimer were found to be associated with mortality. Close monitoring of these parameters during the follow-up and treatment of patients may provide additional benefits in terms of survival. Our study enriches what we know about COVID-19 infection in HD patients by supporting the literature and with different points from the literature.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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