COVID-19 IN HEMODIALYSIS PATIENTS: THE RELATIONSHIP BETWEEN AGE AND SURVIVAL

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ABSTRACT

Introduction*: Because uremia and aging are associated with the impairment of lymphocyte and granulocyte function, the reduced immune response in elderly patients undergoing hemodialysis with chronic renal failure may adversely affect the response to SARS-CoV-2 infection. This study aimed to evaluate the relationship between survival and age and other prognostic factors in patients with COVID-19 undergoing hemodialysis.*

Materials and method*s: The demographic, clinical, laboratory, and radiological data of patients with chronic renal failure who underwent hemodialysis treatment and had a positive polymerase chain reaction test for SARS-CoV-2 were retrospectively reviewed. The study group was divided into two groups: patients aged 59 and below and those aged 60 and above.*

Results*: Analyses of all patients in our study revealed that the mortality rate was 16.6%, while it was 23.7% in the group aged 60 years and above. The most common symptoms observed in patients aged 60 years and above were muscle-joint pain, respiratory distress, and cough. Evaluation of surviving and deceased patients demonstrated that the advanced age, male sex, and presence of respiratory distress were significantly associated with death. A decrease in lymphocyte, thrombocyte, and albumin levels and an increase in neutrophil, urea, C-reactive protein, procalcitonin, D-dimer, and troponin levels were reported in patients who died; this difference was statistically significant.*

Conclusion*: Thus, these data show that previous kidney disease may be a risk factor for a more severe course of COVID-19, particularly in elderly patients. Implementation of infection control measures and prevention of disease transmission should be the primary goal.*

Keywords: *COVID-19, Hemodialysis, Age, Chronic renal failure, Elderly, Survival.*

DOI: 10.19193/0393-6384_2021_3_209

Received *November 15, 2020;* ***Accepted*** *March 20, 2021*

Introduction

In December 2019, an outbreak of the coronavirus disease 2019 (COVID-19) caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, China, and rapidly spread to other provinces of China and throughout the world[1]. To date, no antiviral drug has proven effective for treating patients with COVID-19. Supportive therapy is the main treatment approach for managing symptomatic patients who require mechanical ventilation and other intensive care services[2].

T cell immunity has been confirmed to be a key factor against SARS-CoV-2 infection[3]. Aging is associated with various physiological changes and progressive decline in physiological homeostasis, both of which lead to organ function changes, multimorbidity, and frailty. Age-related changes in the immune system, called immunosenescence, influence an organism's ability to cope with external stressors. Although the total number of neutrophils

remains unchanged with advancing age, it has been shown that their phagocytic ability decreases with age. T cells are also affected by the aging process[4].

Since uremia is associated with extensively impaired lymphocyte and granulocyte function, the reduced immune response in advanced elderly patients undergoing hemodialysis (HD) for chronic renal failure (CRF) may negatively affect the response to SARS-CoV-2 infection[5]. However, patients who undergo maintenance HD for CRF, typically three times a week, should continue to undergo this therapy to survive. These patients may be at high risk for COVID-19 infection and its adverse consequences due to aging, uremia, and many comorbid conditions[6].

This study aimed to evaluate the relationship between survival and age and other prognostic factors in HD patients diagnosed with COVID-19.

Materials and methods

In this study, all patients over the age of 18 undergoing HD treatment three times a week for CRF who were admitted to Fethi Sekin City Hospital with positive RT-PCR tests for SARS-CoV-2 from March 18, 2020, when the first COVID-19 case was detected in our city, to December 31, 2020, were included.

Age, sex, history of chronic disease including diabetes mellitus (DM), hypertension (HT), and congestive heart failure (CHF), history of contact with patients diagnosed with COVID-19, and clinical symptoms at the time of admission (fever, cough, respiratory distress, muscle-joint pain, headache, taste-odor disorder, nausea-vomiting, and abdominal pain-diarrhea) were recorded. Radiological results of the lungs and biochemical and hematological values, including white blood cell (WBC) count, hemoglobin (Hb), platelet (PLT) count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), and levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, C-reactive protein (CRP), procalcitonin (PCT), ferritin, troponin, and D-dimer were retrospectively retrieved from the hospital automation system and patient medical records. In addition to the positive RT-PCR results, the concurrent examination results of the outpatients and the examination results of the hospitalized patients at the time of hospitalization were recorded. Radiological results of the lungs were assessed with and without evidence of pneumonia.

Patients undergoing hemodialysis were divided into two groups based on age: patients aged 59 and below and patients aged 60 and above. All patients were treated in accordance with the recommendations of the Turkish Ministry of Health COVID-19 (SARS-CoV-2 Infection) Adult Patient Treatment Guidelines[7]. COVID-19 patients on hemodialysis for conditions other than CRF, those who had undergone immunosuppressive therapy, those with malignancy, and those with uncontrolled additional chronic diseases were excluded.

This study was designed in accordance with the World Medical Association Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects. Permission was granted by the Scientific Research Board of the Directorate General of Health Services affiliated to the Republic of Turkey Ministry of Health, and approval was obtained from the local ethics committee.

Statistical Analysis

All statistical analyses were performed using IBM SPSS software ver. 22.0. The Shapiro-Wilk test was used to test the assumption of normality of the data. Descriptive statistics of the data are presented as mean ± standard deviation for variables with normally distributed continuous data, median (minimum–maximum) for non-normally distributed continuous data, and frequency (percentage, %) for categorical variables. The Mann-Whitney U test was used in the comparison of two groups for normally distributed continuous data. The Pearson chi-square test was used to evaluate categorical data. A P-value of <0.05 was considered statistically significant.

Results

The RT-PCR test results of all 54 patients included in the study were positive. Sixteen (29.6%) patients were aged 59 years and below, and 38 (70.4%) were 60 years and above. The mean age of all patients was 62.29 ± 10.82.

The age range was 39–59 years, with a mean age of 48.81 ± 6.05 for the group of patients who were 59 years and below. Nine (56.3%) of these patients were female, and seven (53.7%) were male. Twelve (75%) of the patients had additional diagnoses for chronic diseases other than CRF. The most common additional chronic disease was diabetes mellitus, seen in nine (56.3%) patients. All patients had one or more clinical signs associated with COVID-19. The most common clinical symptom in this group was muscle-joint pain in 13 (81.3%) patients. Moreover, 5 (31.3%) patients had a history of con-

tact with patients diagnosed with COVID-19. No patient died in this group, and the survival rate was 100% (Table 1).

	Aged 59 and below n(%)	Aged 60 and above n(%)	Death n(%)	Survival n(%)
Age	**P***		**P****	
(Ort.±St.S.)	48,81±6,05	67,97±6,43	69±5,76	60,95±11,4
Sex			**P**=0,027**	
Male	7 (43,7)	23 (60,5)	8 (88,9)	22 (48,9)
Female	9 (56,3)	15 (39,5)	1 (11,1)	23 (51,1)
Life	**P*=0,033**			
Survival	16 (100)	29 (76,3)		
Death	0 (0)	9 (23,7)		
Chronic additional disease				
Positive	12 (75)	29 (76,3)	8 (88,9)	33 (73,3)
Negative	4 (25)	9 (3,7)	1 (11,1)	12 (26,7)
Hypertension				
Positive	8 (50)	21 (55,3)	6 (66,7)	23 (51,1)
Negative	8 (50)	17 (44,7)	3 (33,3)	22 48,9)
Congestive Heart Failure				
Positive	1 (6,3)	5 (13,2)	1 (11,1)	5 (11,1)
Negative	15 (93,8)	33 (86,8)	8 (88,9)	40 (88,9)
Diabetes Mellitus				
Positive	9 (56,3)	14 (36,8)	6 (66,7)	20 (44,4)
Negative	7 (43,8)	24 (63,2)	3 (33,3)	25 (55,6)
Cough			**P**=0,019**	
Positive	4 (25,0)	19 (50)	7 (77,8)	16 (35,6)
Negative	12 (75,0)	19 (50)	2 (22,2)	29 (64,4)
Respiratory distress	**P*=0,012**		**P**=0,036**	
Positive	5 (31,3)	26 (68,4)	8 (88,9)	23 (51,1)
Negative	11 (68,8)	12 (31,6)	1 (11,1)	22 (48,9)
Muscular-Joint Pain				
Positive	13 (81,3)	27 (71,1)	5 (55,6)	35 (77,8)
Negative	3 (18,8)	11 (28,9)	4 (44,4)	10 (22,2)
Fever	**P*=0,012**			
Positive	10 (62,5)	10 (26,3)	4 (44,4)	16 (35,6)
Negative	6 (37,5)	28 (73,7)	5 (55,6)	29 (64,4)
Headache			**P**0,006**	
Positive	8 (50)	14 (36,8)	0 (0)	22 (48,9)
Negative	8 (50)	24 (63,2)	9 (100)	23 (51,1)
Nausea-vomiting				
Positive	7 (43,8)	10 (26,3)	1 (11,1)	16 (35,6)
Negative	9 (56,3)	28 (73,7)	8 (88,9)	29 (64,4)
Taste-odor disorder				
Positive	1 (6,3)	6 (15,8)	0 (0)	7 (15,6)
Negative	15 (93,8)	32 (84,2)	9 (100)	38 (84,4)
Abdominal Pain-Diarrhea				
Positive	4 (25)	5 (13,2)	0 (0)	9 (20)
Negative	12 (75)	33 (86,8)	9 (100)	36 (80)
History of contact	**P*=0,003**			
Positive	5 (31,3)	28 (73,7)	4 (44,4)	29 (64,4)
Negative	11 (68,8)	10 (26,3)	5 (55,6)	16 (35,6)
Antibiotic use				
Positive	12 (75)	32 (84,2)	9 (100)	35 (77,8)
Negative	4 (25)	6 (15,8)	0 (0)	10 (22,2)

Table 1: Attitudes and behaviors of patients during the pandemic.

p: Comparison between aged 59 and below and aged 60 and above groups, p**: Comparison between death and survival groups*

For the group aged over 60 years, the age range was 60-86 years with a mean age of 67.97 ± 6.43 years. Furthermore, 15 (39.5%) of these patients were females and 23 (60.5%) were males. Moreover, 29 (76.3%) patients had one or more additional chronic diseases other than CRF. The most common additional chronic disease was hypertension, seen in 21 (55.3%) patients. All patients had one or more clinical signs associated with COVID-19. The most common clinical symptom in this group was respiratory distress, as seen in 26 (68.4%) patients. Furthermore, 28 (73.7%) patients had histories of contact with patients diagnosed with COVID-19. In this group, 9 (23.7%) patients died, and the survival rate was 76.3% (Table 1).

Comparison of the demographic characteristics and clinical variables of the patients revealed that respiratory distress and contact history were significantly higher (p = 0.012 and p = 0.003, respectively) and fever was significantly lower (p = 0.012) in the group aged 60 and above compared to the group aged 59 and below. There was no death in the group aged 59 and below; when survival rates were compared, a statistically significant difference was observed between the two groups (p = 0.033). No statistically significant difference was observed when the other variables were compared (Table 1).

In evaluating the demographic characteristics and clinical variables of the surviving and deceased patients, male sex, presence of cough, respiratory distress, and age over 60 years were associated with death, rather than survival (p = 0.027, p = 0.019, p = 0.036 and p = 0.033, respectively) (Table 1).

	Aged 59 and below	Aged 60 and above	Death	Survival
	P*		**P****	
WBC Medyan(Min-Maks)				
$x10^3$	5,5(2,27-11,4)	6,4(2,44-16,4)	9,5(2,98-16,4)	5,5(2,27-14,2)
Nötrofil			**P**=0,027**	
$x10^3$	4,29(2-9,28)	4,15(1,44-14,79)	7,5(2,71-14,79)	4,14(1,44-11,93)
Lenfosit			**P**=0,020**	
	600(220-1340)	770(110-1600)	560(110-970)	800(220-1600)
Nötrofil/Lenfosit ratio			**P**=0,000**	
	6,66(1,51-38,64)	6,15(1,73-27,95)	15,88(5,1-27,9)	5,82(1,5-38,6)
Hemoglobin				
	10,25(7,5-13)	11(5,7-14)	9,6(5,7-13,4)	10,6(7,5-14)
Platelet			**P**=0,000**	
$x10^3$	181(57-614)	156,5(83-611)	114(83-134)	176(57-614)
Üre			**P**=0,022**	
mg/dL	99,5(39,2-175)	102,6(44,2-246)	165,1(87,8-238)	101,6(39,2-246,2)
Kreatinin	**P*=0,004**			
mg/dL	5,51(4,06-13,5)	7,13(4,24-11,4)	6,94(5,2-11,4)	6,7(4,06-13,5)
AST				
U/L	21(10-55)	28(13-134)	23(14-44)	26(10-134)
ALT				
U/L	14,5(6-26)	15(4-56)	11(4-53)	15(5-56)
Albumin			**P**=0,002**	
g/L	35,5(28-44)	32,5(21-44)	28(24-33)	34(21-44)
Ferritin				
µg/L	764(80-1500)	1276(52-1500)	1400(264-1500)	1072(52-1500)
Troponin			**P**=0,004**	
ng/L	17,6(2,9-76,2)	27,26(4,9-1274)	47,7(29,6-682,2)	17,1(2,9-1274)
D-dimer			**P**=0,003**	
ng/L	1015(380-5240)	1085(218-10x10^3)	3310(878-10x10^3)	990(218-5610)
Procalsitonin			**P**=0,012**	
µg/L	0,43(0,06-8,4)	1,51(0,01-45)	3,5(0,2-45)	1i2(0,01-17,6)
CRP	**P*0,005**		**P**=0,000**	
mg/L	14,8(1-161)	62,2(4-412)	204(52-412)	32,6(1-287)
Torax BT			**P**=0,042**	
Positive n(%)	9 (56,3)	30 (78,9)	9 (100)	30 (66,7)
Negative n(%)	7 (43,8)	8 (21,1)	0 (0)	15 (33,3)

Table 2: Comparison of groups according to laboratory findings.

Descriptive values are given as Medyan(Min-Maks) in the table. p: Comparison between aged 59 and below and aged 60 and above groups; p**: Comparison between death and survival groups*

Table 2 summarizes the comparison of patients in both groups according to their hematological and radiological biochemical results. When the hemato-

logical and biochemical results of the groups were compared, a statistically significant increase was observed in the creatinine and CRP values in the group aged 60 and above compared to the group aged 59 and below ($p = 0.004$, $p = 0.038$, and $p = 0.005$, respectively). No significant differences were observed when other variables were compared (Table 2).

While neutrophil count, neutrophil/lymphocyte ratio, urea, troponin, D-dimer, procalcitonin, and CRP were significantly higher among patients who died than among those who survived ($p = 0.027$, $p = 0.000$, $p = 0.022$, $p = 0.004$, $p = 0.003$, $p = 0.012$, and $p = 0.000$, respectively), lymphocyte count, platelet count, and albumin value were significantly lower ($p = 0.020$, $p = 0.000$, and $p = 0.002$, respectively) (Table 2). The percentage of lung involvement was reported to be significantly higher ($p = 0.042$) in patients who died than in those who survived ($p = 0.042$). No statistically significant difference was observed when the other variables were compared.

Discussion

There are several studies on CRF patients diagnosed with COVID-19. Our study differs from other studies in that it focuses on age by dividing patients undergoing HD for CRF into two age groups with similar demographic and clinical characteristics and additional comorbidities.

The estimates of COVID-19-related survival change as new information is gathered; however, comorbidities such as chronic kidney failure, cardiovascular disease, diabetes, chronic respiratory diseases, hypertension, and cancer are associated with poor prognosis. Patients with CRF are known to have a higher risk for upper respiratory tract infection and pneumonia because of their persistent proinflammatory state with functional defects in innate and adaptive immunity. Infections have a significant impact on morbidity in geriatric patients, exacerbate underlying diseases, and are the primary cause of death in one-third of individuals aged 65 and above[8,9].

The World Health Organization (WHO) reported that there are >90 million confirmed cases of COVID-19 worldwide, resulting in 2,014,729 deaths (2.1%). The reported mortality rate for COVID-19 in Turkey was 1.5% in the general population[10]. When all patients were evaluated in our study, the mortality rate was 16.6%, which was 10 times higher than that for the general population. The mortality rate was 0% for those aged 59 and below, and 23.7% for those aged 60 and above.

The mortality rate among patients undergoing HD with an average age of over 60 was 24.9% in Spain[11] and 31% in New York[12]. In a meta-analysis evaluating patients with CRF diagnosed with COVID-19 in China, in which patients were evaluated as either 70 years and above or 70 years and below, the mortality rate in patients over 70 years of age was significantly higher than that in patients under 70 years of age. However, additional chronic diseases other than sex and CRF were not considered in the aforementioned study[13].

Our study differs from other studies since variables, including additional comorbidity and sex, were evaluated and since no differences were observed between our study groups. A striking result in our study was that no deaths were observed in the group aged 59 and below. We could not compare our results to other studies since no study has evaluated the young-middle age group separately. The lower mortality rate in the group with chronic disease and additional comorbidities may be attributed to the relatively limited number of cases in the young-middle age group.

In a meta-analysis, the clinical signs of 3062 patients diagnosed with COVID-19 were evaluated, and 80.4% of these patients had fever, 46% had fatigue, 63.1% had cough, 33% had muscle pain, and 35% had respiratory distress. Nausea-vomiting was reported in 10.2%, diarrhea-abdominal pain in 12.9%, and headache in 15.4%[14]. In another study on COVID-19 patients, fever was observed in 72.4% and respiratory distress in 65.4%, and the rate of antibiotic use in these patients was 74%[15]. In our study, the most common symptoms observed in patients aged 60 and over were muscle-joint pain (71.1%), respiratory distress (68.4%), and cough (50%). The history of antibiotic use was 82.4%. Our results were similar to those reported in the literature.

In our study, the most common symptoms in the group aged 59 and under were muscle-joint pain (81.3%) and fever (62.5%). Fever is the primary symptom of infections; however, fever may be reduced or absent, particularly in one-third of elderly infected patients[8]. In our study, the number of patients with fever was significantly lower in the group aged 60 and above than in the group aged 59 and below.

In our study, 68.4% of individuals aged 60 and above exhibited respiratory distress, while 31.3% of individuals aged 59 and below exhibited respiratory distress. This difference was statistically significant. In the aging lung, significant reductions in physio-

logical capacity may occur because of frequent exposure to environmental toxins and respiratory infections as well as increased stiffness of the chest wall and reduced elasticity of the lung. Because of these factors, elderly people have a higher risk of developing respiratory failure[16].

In our study, the number of patients with a history of contact was higher among patients aged 60 and above compared to patients aged 59 and below. We believe that this may be due to the lack of awareness of infectious diseases in elderly individuals and their inability to protect themselves. Another reason may be that elderly visits have continued, although limited, because of the socio-cultural characteristics of our region.

In a study evaluating elderly and young-middle-aged COVID-19 patients, the CRP value was significantly higher in elderly patients compared to young-middle-aged patients[17,18]. Furthermore, CRP values in patients aged 60 and above were significantly higher than in patients aged 59 years and below ($p = 0.005$). The elevation in CRP values observed in our study was consistent with previous studies. In another study evaluating patients with renal failure diagnosed with COVID-19, it was reported that high serum creatinine value was associated with advanced age[19]. In our study, a significant increase in serum creatinine levels was observed in patients aged 60 and above compared to patients aged 59 and below ($p = 0.004$).

Male sex, advanced age, and respiratory distress have been associated with poor prognosis and mortality in COVID-19 patients. Moreover, decreased levels of lymphocytes, platelets, and albumin, and increased levels of neutrophils, urea, CRP, PCT, D-dimer, and troponin have been considered as predictive biomarkers for poor prognosis and mortality[16,18-21]. In our study, advanced age, male sex, and the presence of respiratory distress were significantly associated with death. The evaluation of surviving and deceased patients revealed that lymphocyte, platelet, and albumin levels were low, whereas neutrophil, urea, CRP, PCT, D-dimer, and troponin levels were elevated, and this difference was statistically significant.

Although RT-PCR testing is the mainstay in diagnosing COVID-19, radiological imaging can be helpful in supporting the diagnosis or in the identification of the pathology. The most frequently reported signs of COVID-19 on chest radiography are lung consolidation and ground-glass opacities[22]. In our study, 56.3% of patients aged 59 and below, 78.3% of patients aged 60 and above, and all patients who died had radiologically proven lung involvement. This difference was statistically significant.

The main limitation of our study is the low number of cases because it was conducted in a single center and comprised of a special patient group. Another limitation is that there is no data regarding disease stage, course of the disease, and the drugs administered to treat CRF and other chronic diseases.

Elderly individuals diagnosed with CRF are highly susceptible to death due to COVID-19. Therefore, they require special care during infection with COVID-19, starting from the prevention of the infection through to during the diagnosis, treatment, and recovery period, and even afterwards. There should be a specific protocol for follow-up and treatment, particularly for elderly patients with chronic disease, initiated the instant COVID-19 symptoms first appear Preliminary data have shown that previous kidney disease may be a risk factor for a more severe course of disease, especially in elderly patients. Elderly individuals who undergo HD treatment for CRF are highly vulnerable to COVID-19. The primary aim should be to prevent or minimize the transmission of the disease by taking appropriate infection control measures, and we believe it would be appropriate to prioritize this group during vaccination.

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