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Role of the inflammatory activity in haemodialysis patients with COVID-19

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ABSTRACT

Objectives: It is known that haemodialysis (HD) patients are older and have more co-morbidities, and therefore they are very susceptible against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Inflammatory activity plays an important role in coronavirus disease 2019 (COVID-19), and the intensity of inflammatory response makes the severity of COVID-19 worse. Biomarkers related to infection such as procalcitonin (PCT), C-reactive protein (CRP), ferritin, albumin, troponin I, D-dimer, white blood cell (WBC), neutrophil, lymphocyte, and platelet play an important role in the inflammatory response of COVID-19. Our objective is to compare these biomarkers between healthy individuals with COVID-19 (HI-COVID-19) and haemodialysis (HD) patients (HP-COVID-19).

Methods: 50 patients diagnosed with COVID-19 were included in this cross-sectional and monocentric retrospective study. The population of this study was separated into two groups: Group 1 consisted of HI-COVID-19 (n=27), and Group 2 consisted of HP-COVID-19 (n=23). Demographic data, basic clinical characteristics, and laboratory tests were recorded during the application. Group 2 participants were chosen from those whose biomarkers such as ferritin (<200 ng/mL), CRP, PCT, ferritin, albumin, D-dimer, troponin I, WBC, neutrophil, lymphocyte, and platelet were within the normal range three months before (prior to having COVID-19).

Findings: When Group 2 and Group 1 were compared in terms of gender, age, presence of lung uptake, and fever, there was no difference. Five HP-COVID-19 patients lost their lives. There were no deaths in the other group. There was a statistically significant difference. Comorbid diseases such as diabetes mellitus (DM), coronary artery disease (CAD), and hypertension (HT) were significantly higher in Group 2. It was observed that CRP, PCT, troponin I, D-dimer, and ferritin from biochemical parameters were higher in Group 2, and platelet and albumin were higher in Group 1. Although WBC and neutrophil elevations and low lymphocytes were detected in Group 2, it was statistically not significant. Tocilizumab and convalescent plasma use were significantly higher in Group 2.

Conclusions: The strength of inflammatory activity in HP-COVID-19 can be estimated by observing serum levels of biomarkers such as CRP, PCT, ferritin, albumin, D-dimer, troponin I, WBC, neutrophil, lymphocyte, and platelet.

Keywords: Haemodialysis, Coronavirus Disease 2019, C-reactive protein, procalcitonin, lymphocyte

INTRODUCTION

Novel Coronavirus Disease 2019 (COVID-19), which has evolved from the infection with Severe Acute Respiratory Syndrome Coronavirus 2 Virus (SARS-CoV-2), outbreaked in Wuhan, China, in December 2019. COVID-19 has rapidly spread to the other parts of China and other countries (1,2). Kidney failure is a violent medical situation with a high prevalence of comorbid conditions, including heart disease and diabetes mellitus (DM), which heavily affect the elderly(3). According to the China National Data System (4), 579,381 haemodialysis (HD) patients were reported in 2018, with 33,795 of them in Hubei Province. Patients with HD have a higher sensitivity to SARS-CoV-2 pneumonia than the general population since they are old and have more medical history. While most patients had asymptomatic or only mild symptoms, approximately 15-20% of them required hospitalization, and less than 5% of them developed severe illness,

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which is the manifestation of acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF), for which intensive care support is generally required and frequently provide a poor prognosis (5). The pathophysiology of COVID-19 is not entirely defined yet, and the lack of effective treatments creates a need to urgently enforce novel therapeutic strategies which will be developed by considering the pathophysiological assumptions. By binding angiotensin-converting enzyme-2 to human cells, the SARS-CoV2 spike protein induces cellular infection (6). The inflammasome in the host cell is activated by cellular infection and viral replication, resulting in the release of pro-inflammatory cytokines and cell death due to the pyroptosis, with the following release of a damage-related molecular pattern that amplifies the inflammatory response (7, 8). In COVID-19, one of the systems that result in ARDS and MOF is excessive cytokine release in response to viral infection, often known as cytokine release syndrome or cytokine storm (7). However, the cytokine release and inflammatory response in severe COVID-19 is currently known as incompetent.

Inflammatory activities and cytokine release of the individuals who do not have any diseases and those who have chronic kidney disease (CKD) and receive HD (with comorbid diseases) were reacted differently when they fell ill with COVID-19. It is possible that the severity of COVID-19 disease is affected by this difference. When the literature is examined, it is concluded that the HPs-COVID-19 and HIs-COVID-19 were not compared in terms of inflammatory activities and cytokine storm. In this regard, to our knowledge, this study will be the first in the literature. Our aim in this study was to compare these two groups in terms of the serum levels of the biomarkers associated with infection, such as CRP, PCT, ferritin, albumin, D-dimer, troponin I, WBC, neutrophil, lymphocyte, and platelet.

MATERIAL and METHODS

Patients and methods

Study groups: In this study, all participants were divided into two different groups by us.

Group 1: The inclusion criteria were healthy individuals who had COVID-19 (HIs-COVID-19); among the 1300 patients who were admitted to our Infectious Diseases and Clinical Microbiology Clinic, 27 HIs-COVID-19 patients were selected as healthy individuals with COVID-19. Data such as population characteristics and clinical and biochemical data were recorded following patient admission. The exclusion from the HIs-COVID-19 group were the patients with neoplastic diseases, hypertension (HT), cardiovascular diseases, CKD, asthma, obesity diseases, chronic obstructive pulmonary disease (COPD), DM, hematologic diseases, inflammatory disorders, smokers, and under herbal/drug therapy.

Group 2: Haemodialysis patients with COVID-19 (HD-COVID-19) formed the second group of our study. In addition, the 23 HPs-COVID-19 were also selected from 150 patients and accepted into our nephrology clinic. Data such as population characteristics and clinical and biochemical data were recorded following patient admission.

The inclusion criterion for HD-COVID-19 was that the patient had undergone CKD and continued to receive HD therapy for six months. Etiological causes of the kidney disease in Group 2 can be listed as follows; DM, HT, coronary artery disease (CAD), iatrogenic cause, kidney stone, glomerulonephritis, and Fabry disease. There was also a patient with a history of cerebral vascular obstruction (CVO). In this study, patients with acute renal impairment were excluded. Users of angiotensin converting enzyme inhibitors and angiotensin receptor inhibitors were not included in this study. We have selected the participants in Group 2 among those with the biomarkers, such as ferritin (<200 ng/mL), CRP, PCT, ferritin, albumin, D-dimer, troponin I, WBC, neutrophil, lymphocyte, and platelet within the normal range up to three months ago (before falling ill with COVID-19).

Laboratory tests: Patient data, as well as routine biochemical parameters, complete blood count, and demographics, were extracted from available medical records. Blood samples were collected after a twelve-hour fasting period. WBC, neutrophil, lymphocyte, and platelet analyses were conducted using blood samples that had been collected in tubes with EDTA, using an automatic blood counter (Mindray BC6800 Auto Haematology Analyzer Device [Shenzhen Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, P.R, China]).

Biochemical biomarkers, such as serum glucose, urea, creatine (Cre), albumin, lactate dehydrogenase (LDH), and CRP, were analyzed by spectrophotometer, using a Beckman Coulter Chemistry Analyzer AU5800 Device (Beckman Coulter Mishima K.K., Tokyo, Japan).

The fluorescence immunoassay technique was used to conduct an analysis of PCT using a GP Getein 1600 Immunofluorescence Quantitative Analyzer (Getein Biotechnology Co., Ltd. Jiangsu, China).

Ferritin, troponin I, and creatine kinase (CK-MB) were analysed by immunoassay using an ADVIA Centaur XP immunoassay system (Siemens Healthineers, Erlangen, Germany).

D-dimer analysis was conducted using blood samples that had been collected in tubes with Na-citrate (1:9) analyzed with an immunoassay technique using an AQT90 FLEX Immunoassay Analyzer (Radiometer Medical ApS, Bronshoj, Denmark).

Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) analyses were conducted using blood samples that had been collected in tubes with Na-citrate (1:9) and analyzed by the clot, chromogenic, or immune turbidimetric techniques using an STA Compact Max Analyzer (Diagnostica Stago, Asnieres, France)

Statistical Analysis: The analysis was carried out using the SPSS software (version 20.0). Categoric variables have been identified as absolute numbers. In this study, continuous variables were reported as median values or mean ± standard deviation and ranges. Fisher Exact Test, Mann-Whitney U, and Chi-Square Test were used among intragroup comparisons. $P < 0.05$ was found to be statistically significant.

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RESULTS

The study included 50 patients, of which 27 were HIs-COVID-19, and 23 were HPs-COVID-19. Twenty-three of the 150 HD patients who were monitored at our HD center were suffering from COVID-19. Twenty-three of the participants were male, and 27 were female. The average ages of the participants were 63.26±12.2. Forty-three participants had positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR), while the remaining seven were diagnosed due to clinical, laboratory, and radiological analyses; 47 of the participants had positive pulmonary findings. There were no pulmonary results for three participants. Group 2 and Group 1 were compared in terms of gender, age, whether or not pulmonary involvement was present, and whether or not they had a fever, which were found to have no difference. Five HPs-COVID-19 (one female, four males) were deceased. No death was observed in the other group. The difference among the groups was statistically significant.

Dyspnea was significantly present in Group 1. In Group 2, comorbid diseases, such as DM, CAD, and HT, were significantly elevated. Although hospitalization time was longer in Group 2, it was not statistically significant. Whereas all Group 1 members were followed up with hospitalization, nine HPs-COVID-19 were followed up as outpatients. Two HPs-COVID-19 were deceased when they applied to the emergency service. The rest of Group 2 agreed to be hospitalized. The outpatient HPs-COVID-19 recovered within 10 to 15 days on average. While the period between the occurrence of symptoms and the start of treatment or hospitalization was five to seven days for Group 1, it was identified as three to five days for Group 2. The history of contact was statistically significant in Group 1. One HP-COVID-19 was diagnosed with CVO, while another participant had a COPD diagnosis, but it was not statistically significant. Pulmonary involvement was observed with chest computed tomography (CT) in the majority of the two patient groups (excluding two HIs-COVID-19 and one HP-COVID-19). **Table 1** summarizes all participants' demographic and general characteristics.

Table 1: Demographical and general characteristics of all participants

Parameter	Group 1 n:27	Group 2 n:23	p-value
Age (years) (mean±SD)	64.67±8.61	61.61±15.16	0.430
Gender (F/M)	13/14	14/9	0.368
History of contact (no/yes/unknown)	4/22/1	0/13/10	<**0.001****
Did family members contract with COVID-19? (no/yes/unknown)	10/15/2	8/15/0	0.742
Fever (no/yes)	16/11	9/14	0.256
Cough (no/yes)	4/23	4/19	0.805
Dyspnea (no/yes)	7/20	16/7	**0.002***
Hemoptysis (no/yes)	25/2	23/0	0.494
Sputum (no/yes)	26/1	20/3	0.322
Anosmia (no/yes)	25/2	22/1	0.653
Fatigue (no/yes)	0/27	0/23	0.465
Muscle pain (no/yes)	0/27	1/22	0.460
Diarrhea (no/yes)	22/5	15/8	0.196
CAD	27/0	9/14	<**0.001****
HT	27/0	4/19	<**0.001****
DM	27/0	16/7	**0.002***
CVO	27/0	22/1	0.460
COPD	27/0	22/1	0.460
RT-PCR (no/yes)	0/27	7/16	**0.002***
Finding in CT Thorax (no/yes)	2/25	1/22	0.646
Hospitalization (days)	6.89±2.75	9.7±14.88	0.384
Death (no/yes)	27/0	18/5	**0.003***
Tocilizumab (Using/Not Using)	1/27	7/16	**0.004***
Convalescent plasma (Using/Not Using)	1/27	6/17	**0.003***

**<0.001, *<0.05, CAD, coronary artery disease; HT, hypertension; DM, diabetes mellitus; CVO, cerebrovascular obstruction; chronic obstructive pulmonary disease (COPD); RT-PCR, real-time reverse transcriptase-polymerase chain reaction; CT, computerized tomography.

Table 2: Symptoms and findings of all participants

Parameter	No (n, %)	Yes (n, %)
Fever	25 (50)	25 (50)
Cough	8 (16)	42 (84)
Dyspnea	23 (46)	27 (54)
Hemoptysis	48 (96)	2 (4)
Sputum	46 (92)	4 (8)
Anosmia	47 (94)	3 (6)
Fatigue	0	50 (100)
Muscle pain	1 (2)	49 (98)
Diarrhea	37 (74)	13 (26)

Fever, cough, dyspnea, fatigue, and muscle pain occurred in most patients. The primary symptom in the patients was fatigue. Hemoptysis, sputum, anosmia, and diarrhea were the least observed symptoms. Symptoms and outcomes for all participants are summarised in T**able 2**.

Although WBC, neutrophil, and low lymphocyte elevations were found in Group 2, they were not statistically significant. While the parameters such as platelet and albumin were identified higher in Group 2, the parameters such as urea, CRP, Cre, PCT, troponin I, D-dimer, and ferritin were identified higher in Group 2. Comparing laboratory parameters across groups is summarized in **Table 3**.

DISCUSSION

Our HD unit is made up of 150 permanent HD patients. A total of 23 of these patients (15.3%) were diagnosed with COVID-19. Five (21.7%) of the 23 HPs-COVID-19 are deceased. In Group 2, co-morbidities were identified as statistically higher.

The ratio of patients deceased due to HD was 3.3%. There were no side effects of HCQ in any of our deceased patients. Among the deceased HD patients, male dominance was prominent (four of the five patients were male and one female), which is consistent with previous studies (9, 10).

All members in groups 1 and 16 of 23 HPs-COVID-19 received positive RT-PCR results. Seven HPs with COVID-19 underwent thoracic CT in addition to respiratory symptoms. The most common defect in chest radiography was the ground-glass opacity, which is similar to the previous reports 9. As documented in the literature, (11) the majority of patients presented with symptoms such as cough, fever, dyspnea, muscle pain, and fatigue.

While all Group 1 members were followed up with hospitalization, fourteen HPs-COVID-19 accepted hospitalization.

Two patients have deceased when they applied to the emergency service. Seven HPs-COVID-19 were followed up as outpatients because they did not agree to be hospitalized. Outpatients recovered over a long period of time, averaging 10 and a half days. The difference between the onset of symptoms and the onset of treatment or hospitalization was less for Group 2. Group 2 was continually hospitalized in our hospital and was diagnosed by medical staff sooner. Recovery plasma and tocilizumab were found to be used primarily in Group 2 (p=0.003, p=0.004, respectively). These findings confirm that the infection process is heavy and that cytokine release is severe in this group of patients. According to Wan et al. (12) cytokine storm is necessary for the development of COVID-19, and as a result, severe complications and the possibility of death.

The fifth edition of "Diagnosis and Treatment of COVID-19" recommends that cytokine levels be carefully monitored in order to improve treatment efficiency and reduce mortality (13).

While not statistically significant, the identification of high and low WBC and neutrophil lymphocytes in Group 2 is consistent with cytokine inflammation and tempest. Hypoalbuminemia, thrombocytopenia, and height in the serum of biomarkers, such as CRP, PCT, ferritin, troponin I, and D-dimer in Group 2 is an indicator of severe inflammation and quick processing of coagulation cascade in this group. The changes in these biomarkers, which play a role in the inflammation process and coagulation cascade, are compatible with the cytokine release and severe inflammation activity.

We will try to explain the general effects of uraemia and kidney disease on the immune system. The uremic toxins may be responsible for acquired immunity disruptions in patients with CKD was reported by the old observation data that uremic serum put into cell cultures reduces T-lymphocyte proliferation after the administration of the stimulation using phytohemagglutinin (14).

Table 3: Laboratory characteristics of all participants

Parameter	Group 1 n:27	Group 2 n:23	P value
Glucose (mg/dL)	107 (79-217)	113 (83-252)	0.514
WBC (x10^9/L)	7.92±4.59	9.07±6.41	0.553
Neutrophile (x10^9/L)	5.91±4.18	7.24±6.04	0.454
Lymphocyte (x10^9/L)	1.38 (0.40-3.36)	1.19 (0.36-7.3)	0.129
Platelet (x10^9/L)	245.40±105.41	155.34±57.21	<**0.001****
Ure (mg/dL)	31 (13-61)	100 (25-62)	<**0.001****
Cre (mg/dL)	0.69 (0.42-1.25)	5.9 (0.1-17)	<**0.001****
Albumin (g/L)	40.16±2.98	33.97±4.64	<**0.001****
LDH (U/L)	318.07±161.60	284.61±104.68	0.599
PCT (ng/mL)	0.02 (0.0-16)	0.8 (0.0-36.61)	<**0.001****
Troponin I (ng/mL)	0.01 (0.0-50)	0.06 (0.0-0.70)	<**0.001****
CRP (mg/L)	13.80 (1.2-114)	85 (4-113)	**0.002***
CK-MB (ng/mL)	0.18 (0-300)	0.68 (0-5)	0.103
D-dimer (µg/L)	384 (111-1170)	1248 (200-5800)	<**0.001****
INR	1.03 (0.0-1.31)	1.1 (0.0-2.5)	0.198
Ferritin (ng/mL)	278.80 (22-1655)	1500 (31-1655)	<**0.001****

**<0.001, *<0.05, WBC, white blood cell; Cre, creatinine; LDH, lactate dehydrogenase; PCT, procalcitonin; CRP, C-reactive protein; CK-MB, creatine kinase-MB; INR, international normalized ratio.

It has been discussed that T-lymphocyte apoptosis has been affected by both the permeability and the composition of the dialysis membrane (15). Acquired immunity disturbances in HD individuals are widespread and varied. They have arisen from complications of chronic renal failure, therapeutic interventions, uremia per se, and HD procedure for their treatment. The present data affirm that these problems of acquired immunity cover the antigen-presenting cell (APC) and T-lymphocyte primarily. While APC is preactivated, the T lymphocyte-dependent immune response is weak, which tends to predispose to infections (16). We emphasized the complex effects of uremia and kidney disease on the immune system. The effects of COVID-19 disease on the immune system are still unknown. We performed this study to solve this mystery.

We will also mention some published studies that are consistent with the findings obtained in this study. Because patients with HD have disarrangements of T- and B-cell function, patients may have uncommon presentations (17, 18). It was reported by Huang et al. (19). that depressed total lymphocytes, high LDH, and prolonged PT levels were reported as the most common laboratory aberrances in COVID-19 pneumonia. Although not statistically significant, serum lymphocyte level in patients with HD was observed as low. (In Group 2, the average serum lymphocyte level was $1.19x10^9$/L, and in Group 1, it was $1.38\ x10^9$/L).

According to Huang et al. (20), a blood albumin level of 35 g/L at presentation increases the probability of death in COVID-19 by at least 6-fold. They proposed that, in addition to lymphocyte count and comorbidities, lower albumin levels on admission can be used to predict the outcome of COVID-19. Group 2 had significantly decreased serum albumin levels ($p<0.001$).

On admission, CRP, PCT, and IL-6 levels increased significantly as 65.0 percent, 5.7 percent, and 67.9% in the patients, respectively. The proportion of patients with elevated levels of IL-6, PCT, and CRP was significantly higher in severe COVID-19 pneumonia than in mild COVID-19 pneumonia, which is consistent with Professor Li Lanjuan's term "cytokine storm", which emphasizes the importance of inflammatory factors in the progression from mild to severe disease (21). Average serum PCT and CRP levels in Group 2 were found significantly lower ($p<0.001$, $p=0.002$, respectively).

Serum ferritin, characteristic of hemophagocytic lymphohistiocytosis, commonly recognized as a complication of viral infection, is nearly associated with poor recovery of COVID-19 patients, and those with disturbed lung lesions are more probably to have incremented ferritin levels (22). While our patients had ferritin<200 ng/mL before they were fell ill with COVID-19 disease, it increased to an average of 1500 ng/mL during the COVID-19 period ($p<0.001$).

It is demonstrated that patients having an elevated cardiac troponin-I level in the first 24 hours of admission have remarkably higher in-hospital mortality when compared to the patients having a normal troponin-I level. We should note that there are various hypotheses in relation to a myocardial injury that is linked with COVID-19, as represented by high troponin-I compatible with previous observations associated with the outbreaks of the Middle East respiratory syndrome (MERS) and SARS. Microangiopathy, myocarditis, cytokine storm, and myocardial infarction are among these mechanisms (23). In COVID-19 patients, elevated baseline D-dimer levels are linked to inflammation and have a limited predictive value for thrombosis (24). High blood troponin I and D-dimer levels were significant ($p<0.001$, $p<0.001$, respectively) in Group 2, and serum troponin I and D-dimer levels were also found to be extremely high in Group 2 who have deceased.

In Younes Zaid et al. (25) both thrombosis and inflammation are accepted as the clinical manifestations that were monitored during the infection of SARS-CoV-2. They can be fatal, and a better understanding of COVID-19's cellular and molecular effectors could lead to novel therapeutic options for people who are currently not vaccinated. Platelets can interact with viruses, causing thrombosis and inflammation. They looked at platelets in a group of patients with non-severe and severe COVID-19 who had platelet counts in the lower range (but not thrombocytopenic). SARS-CoV-2 RNA appears to be linked to patient platelets, and platelets describe pro-inflammatory chemicals and are hyperactivated in COVID-19, according to their findings. Although the platelets of the Group 2 were observed within the normal range, it was lower than Group 1 ($p<0.001$). This demonstrates that the inflammatory activity was severe.

Our study had certain limitations. The first limitation was that because we had an insufficient number of patients, it is required to conduct a more comprehensive study to generalize the changes in the inflammatory, thrombosis, and coagulation markers that occurred in the patients with HD to all HD patients. The second limitation was that it is required to check serum IL-6, IL-1β, TNF, and IL-10 levels in terms of the cytokine storm or release. We did not evaluate these levels because we do not examine these cytokines in our laboratory. We demonstrated the diagnosis of cytokine release or storm with the clinic and changes in inflammation, coagulation, and thrombosis biomarkers. The third limitation was that because some of our patients with HD did not accept being hospitalized and due to the occasional difficulties in supplying convalescent plasma and tocilizumab, we could not study the role of these treatments in suppressing the cytokine release. However, we mostly used tocilizumab and convalescent plasma in patients with HD.

CONCLUSION

The comorbid diseases-rich HD patients' inflammatory activities and cytokine release were higher when they contracted COVID-19 than individuals without any diseases. Cytokine storm brings about ARDS or MOF, which gives rise to physiological relapse and death. If the serum levels of the biomarkers, such as CRP, PCT, albumin, ferritin, D-dimer, troponin I, WBC, neutrophile, lymphocyte, and platelet, are known and in case of clinical suitability; this may enable us to understand the inflammatory response activity, foresee that the patient may sustain severely and provide the possibility to take the precaution against the complications associated with the COVID-19.

Author Contributions: ZK, FA: Study design, Literature review, Data collection and/or processing, Analysis and/or interpretation, **ZK:** Writing, Revision

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Conflict of interest: The Declaration of Helsinki was followed in this single-center, cross-sectional retrospective investigation upon obtaining consent from the local ethical committee. Informed verbal consent was obtained from all participants.

Ethical approval: The present study was approved by Batman Education and Research Hospital Clinical Research Ethics Committee of Clinical Studies dated 23.03.2021 and 267 decision number.

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