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The Longitudinal Evolution of Post-COVID-19 Outcomes Among Hemodialysis Patients in Turkey

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The Longitudinal Evolution of Post-COVID-19 Outcomes Among Hemodialysis Patients in Turkey

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Methods and cohort

- Turkey
- 47 centers
- Pts on MHD with no past COVID n = 588
- Pts on MHD recovered from COVID n = 635
- Prospective, Observational study

MHD – maintenance hemodialysis

Post-COVID Outcomes		Mortality	Respiratory symptoms	Inpatient status	Oxygen requirement	Lung infection	AVF thrombosis	Thrombo-embolism
Non-COVID MHD	28th day	0.0%	1.9%	4.1%	0.3%	1.4%	0.3%	0.7%
	28-90 day	0.7%	1.7%	3.1%	0.3%	0.7%	0.2%	0.3%
Post-COVID MHD	28th day	3.0%	23.9%	8.2%	4.1%	10.2%	2.0%	2.4%
	28-90 day	2.4%	7.3%	7.1%	1.9%	2.9%	1.5%	1.5%

In multivariable analysis, older age, vascular access type (tunneled catheter) and being in post-COVID period were found as independent parameters related to 90-day mortality.

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Conclusion In the post-COVID period, maintenance HD patients who have had COVID-19 have increased rehospitalization, respiratory problems, vascular access problems, and high mortality compared to the non-COVID HD patients.

The Longitudinal Evolution of Post-COVID-19 Outcomes Among Hemodialysis Patients in Turkey

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The Longitudinal Evolution of Post-COVID-19 Outcomes Among Hemodialysis Patients: A Nationwide Multicenter Controlled Study

BACKGROUND

Hemodialysis (HD) patients have increased risk for short-term adverse outcomes of COVID-19. However, complications and survival at the post-COVID-19 period have not been published extensively.

METHODS

We conducted a national, multicenter observational study that included adult maintenance HD patients recovered from confirmed COVID-19. A control HD group without COVID-19 was selected from patients in the same center. We investigated the characteristics and outcomes in the follow-up of HD patients and compare them with the non-COVID group.

RESULTS

A total of 1223 patients (635 patients in COVID-19 group, 588 patients in non-COVID group) from 47 centers were included in the study. The patients' baseline and HD characteristics were almost similar. 28th day mortality and mortality between 28th day-90th day were higher in the COVID-19 group than non-COVID group [19 (3.0%) patients vs. none (0%); 15 (2.4%) patients vs. 4 (0.7%) patients, respectively]. The presence of respiratory symptoms, rehospitalization, need for home oxygen therapy, lower respiratory tract infection, A-V fistula thrombosis were significantly higher in the COVID-19 group in both the first 28 days and between 28-90 days. In the multivariable analysis, age [Odds ratio (OR) (95% confidence interval[CI]): 1.029(1.004-1.056)], group (COVID-19 group vs. non-COVID group) [OR (95%CI):

7.258(2.538-20.751) and vascular access type (tunneled catheter/AV fistula) [OR(95%CI): 2.512 (1.249-5.051)] were found as independent parameters related to 90-day mortality.

CONCLUSION

In the post-COVID period, maintenance HD patients who have had COVID-19 have increased rehospitalization, respiratory problems, vascular access problems, and high mortality compared to the non-COVID HD patients.

Key words: Hemodialysis, COVID-19, Outcome, Nationwide study

1.INTRODUCTION

Hemodialysis patients have an increased risk for short-term adverse outcomes, such as hospitalization, need for intensive care support, and mortality, of Coronavirus disease 2019 (COVID-19) (1-3). The European Renal Association COVID-19 database (ERACODA), including 768 (72%) dialysis patients, showed that the 28-day probability of death was 25.0% (95% CI 20.2–30.0%) in dialysis patients (4). The data from New York, US, showed 28% in-hospital mortality among hemodialysis (HD) patients(5). Our group showed that undergoing maintenance HD was an independent risk factor for intensive care unit (ICU) admission and in-hospital mortality in Turkey (3, 6).

COVID-19-related symptoms, such as persistent shortness of breath, elevated biomarkers, and abnormalities in chest radiographs, can persist into the late post-COVID periods (7-9). In a study from Wuhan, China describing the main clinical sequelae of 538 COVID-19 survivors, they found that general symptoms (49.6%), respiratory symptoms (39%), cardiovascular-related symptoms (13%), psychosocial symptoms (22.7%), and alopecia (28.6%) might persist for more than three months (10). In a general population cohort, lung-scan abnormalities have been reported in 63% and dyspnea in 16% of patients four months after discharge (9). Post-COVID-19 complications and survival of the patients have not been published extensively among hemodialysis patients. We aimed to investigate the outcomes data, including symptoms, rehospitalization, and mortality in the follow-up of HD patients in the post-COVID-19 period, and compare them with the non-COVID group.

2. MATERIALS AND METHODS

This retrospective study cohort followed the report Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (11). Ethics Committee of Health Sciences University Haseki Training and Research Hospital approved this study (Number: 2020-255).

2.1. Population and setting

We conducted a national, multicenter observational study that included maintenance HD patients aged 18 years or older with confirmed COVID-19. In addition, a control HD group was established from the patients who did not have COVID-19 but followed in the same HD center. We did not use historical controls, both to avoid possible bias in selection and to exclude possible changes in the quality of care and treatment that might cause differences in the outcomes in all HD patients that may occur during the COVID-19 pandemic. Instead, control participants were chosen as the patient who had started dialysis closest in time to the COVID-19 patient at each center. A web-based database was specifically designed to collect the data. This study has included the data recorded in this database from April 21, 2021 to June 11, 2021.

The main database included only patients' whose severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcriptase-polymerase chain reaction (RT-PCR) test became negative and were not receiving any antiviral treatment for COVID-19 and had data from at least 28 days after diagnosis of COVID-19. We included patients who had confirmed SARS-CoV-2 infection based on positive RT-PCR testing of a nasopharyngeal swab. We did not include patients in the acute period of COVID-19 (SARS-CoV-2 RT-PCR still positive and/or still receiving antiviral treatment for COVID-19). The peritoneal dialysis patients or kidney transplant recipients, patients undergoing temporary HD due to acute kidney injury were not included. SARS-CoV-2 RT-PCR negative COVID-19 patients and the patients without outcome data were excluded.

2.2. Measurements and definitions

We recorded demographic data, comorbidities and medications, primary kidney diseases that cause end-stage renal disease (ESRD), duration of HD, vascular access type, residual urine

amount, dialysis membrane surface area, data regarding HD sessions [predialysis weight, systolic and diastolic blood pressures, mean erythropoietin stimulating agents (ESA) dosage, Kt/V, urea reduction rate (URR), mean ultrafiltration volumes per sessions, venous pressures and speed of HD pump]. We also collected data regarding routine lab tests [hemogram, serum creatinine, electrolytes, alanine aminotransferase (ALT), albumin, C-reactive protein (CRP), ferritin] at the last monthly routine check before the development of COVID-19. The same lab tests were also obtained in the same monthly check for the non-COVID group. In addition, we obtained data for presenting symptoms, the COVID-19 treatment, presence of pneumonia at computerized chest tomography (CT) and ICU admission, mechanical ventilation, and main treatments in ICU for the COVID-19 group.

We have classified COVID-19 patients according to the clinical severity of the disease at presentation according to the Ministry of Health guideline (12): patients with no symptoms and/or detected at screening were classified as an *asymptomatic disease*; if there is fever, cough, etc., but no dyspnea-(there may be abnormal finding on CT) were called *mild disease*; if there is dyspnea requiring oxygen administration-(maybe other symptoms together) were called *moderate-severe disease*; and blood arterial oxygen saturation <90% despite oxygen support at admission or hemodynamic disorders requiring ICU follow-up were classified as a *serious life-threatening disease*.

2.3 Follow-up and Outcome

The primary endpoints in the study were dead within 28 days, and between 28-90 days. The secondary composite endpoints included rehospitalization, the persistence of respiratory symptoms associated with COVID-19, and the development of lower respiratory system infection or vascular access problems (thrombosis or catheter placement) within the 90 days after diagnosis of COVID-19. For the non-COVID group patients, primary and secondary

endpoints were also questioned during the same period (28 and 90 days) and compared with the COVID-19 group.

2.4 Statistical Analyses

IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The normality of variables was decided using visual methods (histograms and probability plots) and Kolmogorov-Smirnov tests. We presented numbers and percentages for categorical variables, median and interquartile ranges (25-75%) for numeric variables in descriptive statistics. The chi-square test was used for two or multiple group comparisons of categorical variables. We used the independent t-test or Mann-Whitney U test as appropriate in the comparison of numerical variables. In the multiple group comparisons of numerical variables, we used the variance (ANOVA) test for numerical variables with normal distribution and the Kruskal-Wallis test for numerical variables that were not normally distributed. To determine the independent parameters related to the 90th-day mortality, a multivariable binary logistic regression model with “enter” method was used, including the different parameters between non-survivors and survivors. The missing data were considered as pairewise missing in the analyses and were not imputed in the study. $P < 0.05$ was accepted as the level of significance.

3. RESULTS

1. Demographic and Baseline Characteristics:

The main database had 1362 patients from 47 centers in Turkey. We excluded patients with a negative RT-PCR test (n=85 patients), patients without a non-COVID group from that center (8 patients), duplicated records (8 patients), patients with missing primary outcome data (3 patients), and active COVID-19 patients (35 patients). The remaining 1223 patients (635 COVID-19 group, 588 non-COVID group) were included in the study.

The median age of the COVID-19 group was 58.9+14.8 years (min-max: 19-93), the median age of the non-COVID group: 57.1+15.4 years (min-max: 18-94). The number of women was 292 (45.9%) in the COVID-19 group and 239 (40.7%) in the non-COVID group. Table 1 and Supplementary Table 1 represents the patients' baseline demographics, comorbidities, HD-related data, baseline, first and third-month laboratory tests. The most common cause of ESRD was diabetic kidney disease in the COVID-19 group (36.2%) and hypertensive nephrosclerosis in the non-COVID group (36.9%). The presence of comorbidities, medicines and smoking status of the groups were not statistically different. The rates of medication use were consistent with the rate of comorbidities.

2. HD related data of the groups

The median HD duration of the COVID-19 group was 48 (IQR: 24-96) months and 53 (IQR: 24-96) months in the non-COVID group (Supplementary Table 1). The most common vascular access type was A-V fistula in both groups. However, this rate was significantly higher in the non-COVID group than the COVID-19 group (82.8% vs. 76.9%, respectively). Tunneled HD catheter rate was significantly higher in the COVID-19 group than the non-COVID group (20.3% vs. 15.1%, respectively). Predialysis weights, residual urine volumes, blood pressures,

duration of the sessions, ultrafiltration volumes, blood pump rate, venous pressures, rate of ESA usage, used anticoagulant types were not different between the groups. Kt/V, URR, and dialyzers surface areas were significantly lower in the COVID-19 group than the non-COVID group [1.56 (IQR: 1.40-1.75) vs. 1.60(IQR: 1.40-1.80); 72%(IQR: 68-77) vs. 74%(68-78) and 1.7(1.6-1.8) vs. 1.8(IQR: 1.7-1.8), respectively].

Predialysis serum creatinine in the COVID-19 group was significantly lower. CRP, ferritin, and leukocyte counts were significantly higher than the non-COVID group (Table 1). All other lab tests were not different between the groups.

3. The data regarding COVID-19

Table 2 represents the data of COVID-19 in the COVID-19 patients during the active period of the disease. 12.3% of the patients were asymptomatic. Fever (67.2%) and cough (63.4%) were the most common presenting symptoms. The total HD session number during the active phase of COVID-19 was 6 (IQR: 5-8). 451 (71.0%) patients in the COVID-19 group were hospitalized due to COVID-19, and 56 (12.4%) of them were admitted to the ICU. Almost half of the ICU admitted patients (n=27, 48.2%) needed mechanical ventilation. The total length of hospital stay was 12 (IQR: 8-18) days.

4. Outcomes at 28th day and between 28th day-90th day

Some characteristics of the patients on the 28th day of the diagnosis of COVID-19 showed significant differences between the groups. The median venous pressure during HD, serum creatinine, potassium, calcium, albumin, and hemoglobin levels were significantly lower in the COVID-19 group (Supplementary Table 2). However, median ESA doses, ALT, ferritin, and CRP levels were significantly higher in the COVID-19 group than the non-COVID group. There were no significant differences in other HD characteristics between the groups. However,

serum CRP, ferritin levels, and leukocyte count were significantly higher in the COVID-19 group.

There were significant differences between the groups regarding the outcomes in this period (Table 3, Figure 1). A total of 19 (3.0%) patients from the COVID-19 group died within the 28th day of the diagnosis of COVID-19. However, none of the patients from the non-COVID group died within the same period. In addition, 28-day mortality was significantly higher in patients with persistent respiratory symptoms than the patients without respiratory symptoms [6/163 (3.7%) versus 1.2% (13/1060), respectively, p=0.018).

A total of 15 (2.4%) patients from the COVID-19 group died between the 28th-90th days of the diagnosis of COVID-19. However, 4 (0.7%) of patients from the non-COVID group died within the same period. Correspondingly, both first 28 days of the disease and between 28-90 days, presence of respiratory symptoms, readmission to hospital for any reason, need for home oxygen therapy, development of lower respiratory tract infection, development of A-V fistula thrombosis, and development of other venous or arterial thromboembolic events, were significantly higher in the COVID-19 group. Although the need for HD catheter insertion was significantly higher in the COVID-19 group within the first 28 days, it was not significantly different between 28th-90th days.

When the characteristics of patients who did not survive were compared with those who survived (Table 4 and Supplementary Table 2), being in the COVID-19 group, age, current smokers, the patients with tunneled HD catheters, presence of dyspnea or coughing at presentation, serious-life threatening disease at presentation, the patients who were given corticosteroids, tocilizumab or anakinra, ICU admission, mechanical ventilation, and using continuous dialysis therapies in the ICU had significantly higher mortality. Moreover, the patients with ongoing respiratory symptoms, rehospitalized patients, the patients needing

oxygen support at home, the patients developing lower respiratory infection within 28 days, and the patients with ongoing respiratory symptoms developing lower respiratory infection between 28-90 days had significantly higher mortality. Mortality was also related to age, serum albumin, CRP levels in the first month, serum albumin, ferritin, and hemoglobin levels in the third month.

In the analysis made according to the date of diagnosis of COVID-19 (Figure 2), we saw that most of the cases occurred in the second half of 2020, with the most deaths in this period. Moreover, we found that the centers showed a similar distribution to this graph in terms of case diagnosis date (Supplementary Figure 1).

We divided the COVID-19 group into outpatient/hospitalized and compared it with the non-COVID group (Supplementary Table 3). Hospitalized patients were older, had more comorbidities, had worse basic laboratory tests, had more COVID-19 symptoms, and had a more severe clinical presentation. All of the deaths on day 28 (all 19 patients) and the majority of deaths between 28-90 days (32 of 38 patients) were from the hospitalized group. Almost all studied clinical problems (any respiratory symptom, rehospitalization for any reason, need of oxygen support at home, lower respiratory infection, AV fistula thrombosis, any other thromboembolic event) on the 28th day and, any respiratory symptom and lower respiratory infection on the 90th day were significantly higher than the other groups.

In the multivariable analysis, age [Odds ratio (OR) (95% confidence interval [CI]): 1.029 (1.004-1.056)], group (COVID-19 vs non-COVID) [OR (95%CI): 7.258 (2.538-20.751) and vascular access type (tunneled catheter vs. AV fistula) [OR (95%CI): 2.512 (1.249-5.051)] were found as independent parameters related to 90 day mortality (Table 5). When this analysis is repeated according to the results of the univariable analysis by dividing the COVID-19 group into two groups according to hospitalization; group (hospitalized COVID-19 vs. non-COVID

group) [OR (95%CI): 7.854 (1.032-59.757) and vascular access type (tunneled catheter vs. AV fistula) [OR (95%CI): 3.522 (1.496-8.292)] were found as independent parameters related to 90th day mortality (Supplementary Table 4).

4. DISCUSSION

In this multicenter retrospective study involving maintenance HD patients recovering from COVID-19 and a non-COVID group, we presented a detailed comparative follow-up data, including demographics, symptoms, laboratory tests, treatments, and outcomes of the groups. One of the most striking findings was significantly higher 28th day and 90th-day mortality in the COVID-19 HD group compared to the non-COVID group. Although the short-term mortality of HD patients with COVID-19 has been shown to be higher than the COVID-19 patients from the general population (3, 13), as far as we know, no study has shown the increased mortality following the acute phase of COVID-19 (post-COVID-19 period) than a non-COVID HD cohort. We showed that all deaths on the 28th day were from the COVID-19 group (3.0% of patients), and most of the deaths (15 of 19) on the 90th day were also from the COVID-19 group, especially among hospital discharged patients. In multivariable analyses, we also found that age, being in the COVID-19 group, and using a tunneled catheter for vascular access were independent parameters related to 90th-day mortality. These data clearly show the ongoing high mortality risk following COVID-19 in HD patients compared to the non-COVID HD patients.

When we compared non-survivors with survivors, being in the COVID-19 group, age, current smokers, the patients with tunneled HD catheters, presence of dyspnea or coughing at presentation, serious-life threatening disease at presentation, corticosteroids, tocilizumab or anakinra use, ICU admission, mechanical ventilation, and using continuous dialysis therapies in the ICU were related with significantly higher mortality. Serum albumin, CRP, ferritin, and

hemoglobin levels were worse in non-survivors. Especially ICU admission and mechanical ventilation were significant predictors of 90th-day mortality, as 26.8% of ICU admitted patients and 59.3% of mechanical ventilated patients died during 90 days. Almost all papers in the literature regarding the outcome of HD patients with COVID-19 included only the acute phase of the disease. As far as we know, this is the first study researching the outcomes of HD patients at the post-COVID period and comparing them with a non-COVID group. Although there are no studies with similar designs and outcomes, some indirect results of studies involving the acute phase of COVID-19 patients may support our outcomes. In a multicenter study of our group including 567 maintenance HD patients with active COVID-19, in-hospital mortality was 16.3% (14). In that study, age (HR: 1.022 [95% CI, 1.003-1.041], p = 0.025), severe-critical disease clinical presentation at the time of diagnosis (HR: 6.223 [95% CI, 2.168-17.863], p < 0.001), presence of congestive heart failure (HR: 2.247 [95% CI, 1.228-4.111], p = 0.009), ferritin levels on admission (HR; 1.057 [95% CI, 1.006-1.111], p = 0.028) were among the risk factors for mortality. In another study conducted by the European Renal Association COVID-19 Database (ERACODA), including 1423 ESRD patients with COVID-19 (HD = 1017 patients/kidney transplant recipients= 406 patients), the higher age, prior smoking history, higher clinical frailty score, and self-reported shortness of breath at first presentation, were identified as predictors of mortality in those discharged at initial triage (15). They also showed that among non-hospitalized patients, 10% (n = 36) were readmitted to the hospital; these patients had worsening respiratory symptoms, a fall in oxygen saturation (97% vs. 90%), and high CRP between attendances (26 vs. 73 mg/L).

Our study gave important data regarding the non-fatal outcomes after the COVID-19. The presence of respiratory symptoms, readmission to hospital for any reason, need for home oxygen therapy, development of lower respiratory tract infection, development of A-V fistula

thrombosis, and development of other venous or arterial thromboembolic events were significantly higher in the COVID-19 group at both first 28 days of the disease and between 28-90 days. We found that dyspnea was reported at a rate of 23.9% on the 28th day and 7.3% on the 90th day of the diagnosis of COVID-19. A similar high prevalence of shortness of breath was reported in the general population after the COVID-19 period. Halpin SJ et al. showed that breathlessness was a significantly higher symptom among patients discharged from ICU than the ward group (65.6% in ICU group and 42.6% inward group), which was assessed 4 to 8 weeks after hospital discharge (16). Although our study included not only hospitalized but also outpatient COVID-19 cases, it seems to be a very significant late persisting symptom. Moreover, among COVID-19 group 4.1% of the patients on the 28th day and 2.9% on 90th-day required oxygen support at home, which was significantly higher than the non-COVID group patients. Moreover, in our study, serum CRP, ferritin levels, and leukocyte counts were significantly higher in the COVID-19 group during follow-ups. The findings of persisting respiratory symptoms, need for oxygen support at home, and development of lower respiratory infections in the COVID-19 group were significantly higher than the non-COVID group. All these might show the ongoing pulmonary inflammation together with the lung sequela of COVID-19 patients.

The rehospitalization rates within 28 days and between the 28th day and 90th day in the COVID-19 group were significantly higher than that of the non-COVID group (8.2% vs. 4.1% and 7.1% vs. 3.1%, respectively). To the best of our knowledge, the rehospitalization rate of HD patients in the post-COVID-19 period has not been published yet. Some studies among non-uremic populations represented comparable data. A retrospective study including the general population cohort aimed to determine 30-day post-hospitalization outcomes following COVID-19 from New York City showed that among 1344 patients, 16.5% returned

to an emergency department, 9.8% were rehospitalized, and 2.4% died(17). In a study from Wuhan, China aiming to describe the long-term health consequences of patients with COVID-19 who have been discharged from hospital, 25 of 1733 patients (1.5%) were readmitted to the hospital (18).

We showed increased AV fistula thrombosis and other arterial or venous thromboses among COVID-19 group patients than the non-COVID group within 28 days and between the 28th and 90th day. During COVID-19, there may be a hypercoagulation condition in which different and complex mechanisms play a role. Microvascular and macrovascular thrombosis with associated inflammation (thrombo-inflammation) ensues commonly in ICU admitted COVID-19 patients (19-21). It has been shown that catheter-related thrombosis is significantly more frequent in COVID-19 patients(22), and having an A-V fistula as vascular access among HD patients might contribute to higher survival of hemodialysis patients with COVID-19(23). However, there is no study showing increased vascular access thrombosis among COVID-19 survivors. A study from France that collected fistula thrombosis cases among active COVID-19 HD patients in seven dialysis units included only 17 patients (24). 10 patients (59%) were men, and 10 patients (59%) were diabetic. The mortality rate in these patients was 47%. All thrombosis were successfully treated with declotting procedures but with an early relapse rate of 36%. Shabaka et al(25). showed increased late thrombotic events in COVID-19 survivors compared to the non-infected cohort after a median follow-up of 7 months (18.5% vs. 1.9%, p = 0.002) among 185 prevalent HD patients. In that study, 6 of 158 patients (3.8%) in the non-COVID-19 group with a previous history of vascular access dysfunction, had vascular access thrombosis 6 months after COVID-19 but none of the COVID-19 group (27 patients) developed vascular access thrombosis.

Another interesting finding of our study is that the predialysis serum Kt/V and URR values of the COVID-19 group before COVID-19 were significantly lower and, CRP, ferritin, and leukocyte counts were higher than the non-COVID group. This may indicate that HD patients with low muscle mass and high inflammation, which may be a component of the malnutrition-inflammation-atherosclerosis complex, may therefore be more susceptible to COVID-19(26).

In our study use of corticosteroids, tocilizumab or anakinra was related to high mortality. All these treatments were given to severe COVID-19 patients according to our national guideline, hence increased mortality in these patients seems to be associated with the severity of the disease. Moreover, to determine the independent parameters associated with the late survival of the patients, we included data that showed significant differences between the patients' baseline demographic data in the multivariable analysis. Age, patient group, vascular access as well as gender and diabetes mellitus, which are promising parameters in the literature, were included in this analysis. In the multivariable analysis, age [OR (95% CI): 1.029 (1.004-1.056)], group (COVID-19 group vs. non-COVID group) [OR (95%CI): 7.258 (2.538-20.751) and vascular access type (tunneled catheter/AV fistula) [OR (95%CI): 2.512 (1.249-5.051)] were found as independent parameters related to 90-day mortality.

In our study, it was seen that there were no patients with serious life-threatening disease in the clinical presentation in the outpatient COVID-19 group, and the rate of moderate-to-severe disease was very low (3.3%) among them. This may be related to the health structure in our country. All HD treatments and, COVID-19 treatments (hospitalizations, ICU admissions-even in private hospitals) in Turkey are covered by the government. All hospitals are allocated to serving pandemic patients as well. In addition, from the onset of the pandemic, there was no problem of finding beds in hospitals or ICUs. CT was readily and easily available and widely used for diagnosis in all patient groups. This study had some limitations.

First, it was retrospective and the groups were not fully randomized. However, the recording of data from different regions in a structured database and the inclusion of a non-COVID group from each center in the study can be considered as close to those encountered in real life. In addition, the fact that our study was designed with simple randomization made the comparisons of the results more valuable. Second, causes of mortality and rehospitalization were not studied in detail, which may provide important data on the causation of COVID-19 complications. However, since COVID-19 is a systemic disease, any cause of death may be associated with COVID-19. Therefore, all-cause mortality may be the best way to evaluate COVID-19-related deaths. In our study, especially the death rate in the non-COVID group seems to be lower than in many other studies. There may be many reasons for this, but the annual mortality rate of chronic HD patients in the Turkish cohort is known to be significantly (up to 50% after adjustments) lower than that published in the US Renal Data System Annual Data Report(27). On the other hand, the annual mortality rates of patients in the Turkish cohort in this study were close to the rates in the Chinese patient cohort published on similar dates(28). This suggests that there may be regional and racial differences.

As a result, in the post-COVID period, maintenance HD patients who have had COVID-19 have increased rehospitalization, respiratory problems, vascular access problems, and mortality compared to the non-COVID HD patients. These adverse outcomes are particularly evident in the post-COVID period of hospitalized COVID-19 HD patients. Thus, longer follow-up of post-COVID 19 in maintenance HD patients may provide further insight into the burden of this infection.

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DISCLOSURE

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Titles/Legends

Supplementary Table 1: The HD-related data and laboratory analyses at first and third months after diagnosing COVID-19 data. All data in the non-COVID group were obtained at the same month with the COVID-19 patient in the non-COVID group.

Supplementary Table 2: Characteristics of survivor and non-survivor patients on the 90th day and differences between the groups.

Supplementary Table 3: The comparative presentation demographics, comorbidities, and laboratory tests of the patients stratified according to hospitalization.

Supplementary Table 4: Binary logistic regression analysis of the baseline parameters related to the 90th-day mortality including COVID-19 group divided into two groups according to hospitalization.

Supplementary Figure 1: Chart showing case distributions and case survivals of centers by COVID-19 diagnosis date

STROBE Statement (pdf)

Supplementary information is available at KI Report's website.

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Table 1: The baseline demographics, comorbidities, and baseline laboratory tests of the patients. All the data were obtained at the month before the development of COVID-19 in the COVID-19 group and the same month in the non-COVID group with the COVID-19 patient.

		COVID-19 Group N: 636	**Non-COVID Group N: 587**	**Total N: 1223**
Demographics				
Age (year), median (IQR)		61(49-70)	60(47-69)	60(48-69)
Gender, n(%)	Women	292(46.0)	239(40.6)	531(43.4)
	Men	343(54.0)	349(59.4)	692(56.6)
Primary kidney disease, n(%)	Diabetic kidney disease	230(36.2)	160(27.2)	390(31.9) *
	Primary Glomerulonephritis	39(6.1)	43(7.3)	82(6.7)
	Hypertensive nephrosclerosis	209(32.9)	217(36.9)	426(34.8)
	ADPCKD	28(4.4)	31(5.3)	59(4.8)
	Other	129(20.3)	137(23.3)	266(21.7)
HD duration (month), median (IQR)		48(24-96)	53(24-96)	48(24-96)
Comorbidities, n (%)				
Diabetes mellitus		276/629(43.9)	196/339(33.5)	472/1214(38.9) *
Hypertension		501/632(79.3)	443/586(75.6)	944/1218(77.5)
COPD		78/621(12.6)	58/583(9.9)	136/1204(11.3)
Cardiac disease		253/624(40.5)	214/582(36.8)	467/1206(38.6)
Cerebrovascular disease		30/612(4.9)	24/581(4.1)	54/1193(4.5)
Malignancy		21/610(3.4)	18/580(3.1)	39/1190(3.3)
Chronic liver disease		17/614(2.8)	21/581(3.6)	38/1195(3.2)
Autoimmune/autoinflammatory diseases		16/611(2.6)	24/578(4.2)	40/1189(3.4)
History of fistula thrombosis		76/599(12.7)	59/581(10.2)	135/1180(11.4)
History of non-fistula thromboembolic disease		15/593(2.5)	13/582(2.2)	28/1175(2.4)
Medicines, n/N (%)				
ACE inhibitor		110/602(18.3)	119/580(20.5)	229/1182(19.4)
ARB		60/605(9.9)	47/576(8.2)	107/1181(9.1)
Calcium channel blockers		277/611(45.3)	236/574(41.1)	513/1185(43.3)
Beta-blocker		278/607(45.8)	238/577(41.2)	516/1184(43.6)
Other antihypertensives		122/600(20.3)	136/575(23.7)	258/1175(22.0)
Insulin		198/615(32.2)	139/581(23.9)	337/1196(28.2) *

Oral antidiabetics		46/609(7.6)	33/579(5.7)	79/1188(6.6)
Statin		119/602(19.8)	99/579(17.1)	218/1181(18.5)
Antiaggregant		315/596(52.9)	311/579(53.7)	626/1175(53.3)
Anticoagulants		142/598(23.7)	116/583(19.9)	258/1181(21.8)
ESA		459/601(76.4)	429/583(73.6)	888/1184(75.0)
IV iron		378/601(62.9)	375/581(64.5)	753/1182(63.7)
Vitamin D or analogs		325/602(54.0)	339/585(57.9)	664/1187(55.9)
Phosphorus binders containing calcium		429/602(71.3)	397/584(68.0)	826/1186(69.6)
Lanthanum		33/578(5.7)	41/580(7.1)	74/1158(6.4)
Cinacalcet		84/578(14.5)	77/580(13.3)	161/1158(13.9)
Smoking, n(%)	Never smoked	352(58.4)	315(56.4)	667(57.4)
	Still smoking	70(11.6)	80(14.3)	150(12.9)
	Quite smoking	181(30.0)	164(29.3)	345(29.7)
Baseline lab data (before COVID-19), median (IQR)				
Potassium (mmol/L)		5(5-6)	5(5-6)	5(5-6)
Calcium (mg/dl)		8.6(8-9)	8.6(8-9)	8.6(8-9)
Phosphorus (mg/dl)		5(4-6)	4.9(4-6)	5(4-6)
Parathormone (pg/mL)		362.55(220-617)	352(193-687)	358(206-646)
ALT (U/L)		11(8-17)	11(7-16)	11(8-16)
Albumin (g/dl)		3.8(4-4)	3.8(4-4)	3.8(4-4)
Ferritin (ng/ml)		533.22(295-868)	492(278-764)	513(289-813)*
CRP (mg/l)		8(3-20)	4(2-11)	5.9(2-15)*
Hemoglobin (g/dl)		11(10-12)	11(10-12)	11(10-12)
Leukocyte(/mm3)		6480(5050-8050)	6230(4800-7900)	6355(4910-7985)*
Number of neutrophils (/mm3)		3850(2600-5400)	3900(2670-5120)	3885(2600-5240)

Abbreviations: HD: hemodialysis, COPD: Chronic obstructive pulmonary disease, ADPCKD: Autosomal dominant polycystic kidney disease, ESA: Erythropoietin-Stimulating Agents, IV: intravenous, ALT: Alanine Aminotransferase, CRP: C reactive protein

*p<0.05

Table 2: The data of COVID-19 in the COVID-19 patients during the active period of the disease.

		N (%)
Symptoms		
Fever		414/616(67.2)
Dyspnea		267/617(43.3)
Cough		391/617(63.4)
Diarrhea		88/604(14.6)
Loss of smell		96/600(16.0)
Loss of taste		111/597(18.6)
Presence of pneumonia at CT		430/563(76.4)
Clinical severity at the time of diagnosis	Asymptomatic disease	78(12.3)
	Mild disease	336(52.9)
	Moderate-to-severe disease	201(31.7)
	Serious-life threatening disease	20(3.1)
Outpatient treatment		185(29.1)
Inpatient treatment		450(70.9)
Treatments for COVID-19		
Hydroxychloroquine		134/586(22.9)
Oseltamivir		33/585(5.7)
Macrolides		121/580(20.9)
Favipiravir		559/613(91.2)
Glucocorticoids		218/586(37.2)
Tocilizumab		8/582(1.4)
Anakinra		5/585(0.9)
Convalescent Plasma		25/583(4.3)
HD place during active period of COVID-19	In another center	85(13.7)
	In attending center	536(86.3)
Changes in HD session during active COVID-19	No changes	20(3.2)
	Isolated room	351(56.9)
	Specific COVID-19 session	223(36.1)
	Other	23(3.7)
Total HD session number during acute phase of COVID-19*		6 (5-8)

Treatment method	Outpatient	185(29.1)
	Inpatient	451(71.0)
ICU data		
ICU Admission		56/451(12.4)
Non-invasive mechanical ventilation		37/53 (69.8)
Mechanical ventilation		27/56(48.2)
ECMO administration		6/54(11.1)
Total length of hospital stay, (days), median (IQR) ¥		12(8-18)

Abbreviations: CT: Computerized tomography, HD: Hemodialysis, ICU: Intensive Care Unit, ECMO: Extracorporeal Membrane Oxygenation

*Median (IQR), ¥ includes ward (+ ICU if applicable)

Table 3: Comparative outcome data of the patients at 28th day and 28-90th day

	COVID-19 group N:635	**Non-COVID group N:588**	**Total N:1223**
28th-day lab data, median (IQR)			
Creatinine (mg/dl)	7.1(5.6-8.7)	7.9(6.3-9.6)	7.5(5.9-9.1)*
Potassium (mmol/L)	4.9(4.4-5.4)	5.1(4.6-5.6)	5.0(4.5-5.5)*
Calcium (mg/dl)	8.5(7.9-9.0)	8.6(8.2-9.1)	8.6(8.0-9.1)*
Phosphorus (mg/dl)	4.8(3.9-5.7)	4.83(3.9-5.8)	4.8(3.9-5.8)
Parathormone (pg/mL)	342(198-600)	365(207-659)	352(200-613)
ALT (U/L)	12(8-18)	11(8-15)	12(8-17)*
Albumin (g/dl)	3.6(3.3-3.9)	3.8(3.6-4.0)	3.73(3.4-4.0)*
Ferritin (ng/ml)	651(357-1026)	505(307-750)	566(328.10-876)*
CRP (mg/l)	10.35(3.70-25.50)	3.4(1.90-11.60)	6.82(2.10-18.0)*
Hemoglobin (g/dl)	10.1(9.00-11.30)	11(10.00-12.00)	10.6(9.47-11.60)*
Leukocyte(/mm3)	6390(4960-7950)	6200(4600-7800)	6300(4815-7850)*
Number of neutrophils (/mm3)	3810(2612-5348)	3910(2770-5040)	3880(2700-5130)
Outcomes, n(%)			
Non-survivor	19(3.0)	0(0)	19(1.6)*
Any respiratory symptom	152(23.9)	11(1.9)	163(13.3)*
Rehospitalization for any reason	52(8.2)	24(4.1)	76(6.2)*
Oxygen support at home	26(4.1)	2(0.3)	28(2.3)*
Lower respiratory infection	65(10.2)	8(1.4)	73(6)*
Urinary tract infection	3(0.5)	6(1)	9(0.7)
AV fistula thrombosis	13(2.0)	2(0.3)	15(1.2)*
Any other thromboembolic event	15(2.4)	4(0.7)	19(1.6)*
Need of HD catheter placement	21(3.3)	9(1.5)	30(2.5)*
28-90th day lab data, median (IQR)	**N:616**	**N:588**	**N:1204**
Creatinine (mg/dl)	7.12(5.7-8.8)	7.9(6.3-9.5)	7.5(5.9-9.1)
Potassium (mmol/L)	5.0(4.5-5.5)	5.0(4.6-5.6)	5(4.6-5.5)
Calcium (mg/dl)	8.7(8.1-9.2)	8.7(8.1-9.1)	8.7(8.1-9.1)
Phosphorus (mg/dl)	5(4.0-5.9)	4.97(4.0-5.90)	5(4.0-5.90)
Parathormone (pg/mL)	324(177-564)	388(215-651)	354(196-600)*

ALT (U/L)	11(8-17)	10(7-15)	11(8-16)
Albumin (g/dl)	3.8(3.5-4.0)	3.8(3.6-4.0)	3.8(3.6-4.0)*
Ferritin (ng/ml)	525(280-888)	476(292-762)	500(288-804)*
CRP (mg/l)	7(3.0-16.0)	4(1.8-11.9)	5.2(2.0-13.7)*
Hemoglobin (g/dl)	11(10.00-11.90)	11.2(10.20-12.00)	11.1(10.10-12.00)
Leukocyte(/mm3)	6415(5080-8030)	6335(4840-7715)	6400(4990-7890)*
Number of neutrophils (/mm3)	3820(2740-5140)	3900(2790-4950)	3845(2769-5040)
Outcomes, n(%)			
Non-survivor	15(2.4)	4(0.7)	19(1.6)*
Any respiratory symptom	45(7.3)	10(1.7)	55(4.6)*
Rehospitalization for any reason	44(7.1)	18(3.1)	62(5.1)*
Oxygen support at home	12(1.9)	2(0.3)	14(1.2)*
Lower respiratory infection	18(2.9)	4(0.7)	22(1.8) *
Urinary tract infection	7(1.1)	7(1. 2)	14(1.2)
AV fistula thrombosis	9(1.5)	1(0.2)	10(0.8)*
Any other thromboembolic event	9(1.5)	2(0.3)	11(0.9)*
Need of HD catheter placement	13(2.1)	10(1.7)	23(1.9)

Abbreviations: AV: Arteriovenous, HD: Hemodialysis

¥ Did not include 19 patients who died before the 28th day

*p<0.05

Table 4: Characteristics of survivor and non-survivor patients on 90th day and differences between the groups.

		Non-survivor N:38	**Survivor N:1185**
Demographics			
*Patient group, n(%)	Non-COVID group	4(0.7)	584(99.3)
	COVID-19 group	34(5.4)	601(94.6)
*Age (year), median (IQR)		68.5(59-74)	60(48-69)
HD duration (month), median (IQR)		48(24-72)	48(24-96)
Gender, n(%)	Women	18(47.4)	513(43.3)
	Men	20(52.6)	672(56.7)
Primary kidney disease, n(%)	Diabetic nephropathy	16(42.1)	374(31.6)
	Glomerulonephritis	1(2.6)	81(6.8)
	Hypertensive nephrosclerosis	11(28.9)	415(35.0)
	ADPCKD	2(5.3)	57(4.8)
	Others	8(21.1)	258(21.8)
Comorbidities, n(%)			
Diabetes mellitus		19(50.0)	453(38.5)
Hypertension		30(78.9)	914(77.5)
COPD		5(13.2)	131(11.2)
Cardiac disease		17(44.7)	450(38.5)
Cerebrovascular disease		2(5.3)	52(4.5)
Malignancy		2(5.3)	37(3.2)
Chronic liver disease		1(2.6)	37(3.2)
Autoimmune/auto-inflammatory disease		1(2.7)	39(3.4)
A-V fistula thrombosis history		5(13.5)	130(11.4)
HD information			
Vascular access, n(%)	*A-V fistula	22(57.9)	953(80.4)
	A-V graft	1(2.6)	19(1.6)
	Catheter (transient)	0(0)	10(0.8)
	*Catheter (tunneled-permanent)	15(39.5)	203(17.1)
Duration of current vascular access (month) , median (IQR)		24.5(18-48)	36(16-72)
Number of sessions during active COVID-19, median (IQR)		6(4-10)	6(5-8)
ICU data, n(%)			
*Admission to ICU		15/32(46.9)	41/420(9.8)
Non-invasive mechanical ventilation		13/15(86.7)	24/38(63.2)

*Need of mechanical ventilation		16/17(94.1)	11/41(26.8)
*ECMO application		0/14(0)	6/40(15)
*Slow continuous treatments (HF/HDF)		6/15(40)	3/40(7.5)
*Total length of hospital stay (including service + ICU), days, median (IQR)		13(8-20)	12(9-17)
Length of stay at ICU, median (IQR)		10(4-17)	8(6-14)
28th day outcomes, n(%)			
*Any respiratory symptoms		16/38(42.1)	147/1185(12.4)
*Rehospitalization		7/38(18.4)	69/1185(5.8)
*Need of oxygen treatment at home		5/38(13.2)	23/1185(1.9)
*Lower respiratory infection		8/38(21.1)	65/1185(5.5)
Urinary tract infection		0/38(0)	9/1185(0.8)
Any venous or arterial thromboembolic events		1/38(2.6)	18/1185(1.5)
A-V fistula thrombosis		1/38(2.6)	14/1185(1.2)
Need of HD catheter		1/38(2.6)	29/1185(2.4)
90th day outcomes, n(%)			
*Any respiratory symptoms		7/38(18.4)	52/1185(4.4)
Rehospitalization		6/38(15.8)	59/1185(5)
Need of oxygen treatment at home		2/38(5.3)	13/1185(1.1)
*Lower respiratory infection		3/38(7.9)	21/1185(1.8)
Urinary tract infection		0/38(0)	14/1185(1.2)
Any venous or arterial thromboembolic events		1/38(2.6)	10/1185(0.8)
A-V fistula thrombosis		0/38(0)	10/1185(0.8)
Need of HD catheter insertion		0/38(0)	23/1185(1.9)

Abbreviations: HD: Hemodialysis, COPD: Chronic obstructive pulmonary disease, A-V: Arteriovenous, ICU: Intensive Care Unit, ECMO: Extracorporeal Membrane Oxygenation, HF: Hemofiltration, HDF: Hemodiafiltration, ADPCKD: Autosomal dominant polycystic kidney disease

*$p<0.05$

Table 5: Binary logistic regression analysis of the baseline parameters related to the 90th-day mortality.

	OR	95% CI for OR		P
		Lower	Upper	
Age (years)	1.029	1.004	1.056	0.026
Gender (male/female)	1.009	0.514	1.983	0.979
Diabetes mellitus	1.116	0.567	2.196	0.751
Group (COVID-19 group /Non-COVID group)	7.258	2.538	20.751	<0.001
Vascular access (Tunnelled catheter/AV fistula)	2.512	1.249	5.051	0.010
Constant	0.004			<0.001

Abbreviations: OR: Odds ratio, CI: Confidence interval, AV: arteriovenous

The model included the parameters that were found different between survivor and non-survivor in Table 4. We also added gender and diabetes mellitus, which might be effective in survival based on the literature.

Legend for the Figure

Figure 1: 28th day and 28-90th day outcome of the groups.

Figure 2: Graph showing case survivals by date of diagnosis of COVID-19