JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Analysis of COVID-19 infection in hemodialysis and kidney transplant patients in a pandemic hospital

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Abstract

Introduction: The mortality rate for any infection is often higher in patients with a kidney transplant (KT) and hemodialysis (HD), which may also be the case in novel coronavirus disease 2019 (COVID-19).

Methodology: In this study, the demographic, clinic, laboratory, and radiologic signs of KT and HD patients diagnosed with COVID-19 infection between 11th March 2020 and 11th March 2021 were evaluated prospectively.

Results: In the present study, 72 HD (median age, 57.5 Q1-Q3:43-65; female: 36/50%) and 58 KT patients (median age, 44.5 Q1-Q3:28.75-55.25; female: 21/36.2%) with COVID-19 infection were enrolled. Fifteen patients with HD (20.8%) died. Age, diabetes mellitus (DM), abnormal hemoglobin levels, albumin, C-reactive protein (CRP), ferritin, D-dimer, and procalcitonin were significant in the univariate analysis of survival in patients with HD. However, only age was significant in the Cox-regression analysis [Hazard ratio (HR) (95% CI 1.070 (19.016-1.126)]. Nine (15.5%) KT patients died. The median time from symptoms onset to admission was three days (2-5). This rate was two (2-3) and five (4-5.75) days, respectively, for patients followed up in our center and the external centers ($p < 0.001$). Although age, DM, shortness of breath, bilateral involvement in CT images, abnormal levels of CRP, urea, leukocyte count, ferritin, and follow-ups of patients from the external center were significant in the univariate analysis of survival in patients with KT, no variables were significant in the cox-regression analysis.

Conclusions: Increased mortality is expected in both HD and KT patients. Early diagnosis of COVID-19 in those patients with COVID-19 infection can be life-saving.

Key words: COVID-19; kidney transplantation; hemodialysis.

J Infect Dev Ctries 2022; 16(6):1016-1024. doi:10.3855/jidc.15829

(Received 19 September 2021 – Accepted 23 March 2022)

Introduction

At the end of 2019, a novel coronavirus, i.e., SARS-CoV-2, was identified as the cause of pneumonia cases in Wuhan, a city in China's Hubei Province. By 2020, it led to a pandemic that has spread worldwide. SARS-CoV-2 disease (COVID-19) primarily manifests as a respiratory tract infection with symptoms ranging from mild upper respiratory infection to severe pneumonia, acute respiratory distress syndrome, and death. COVID-19 disproportionately affects patients with pre-existing comorbidities, and patients with various types of kidney disease are not an exception.

Patients with end-stage renal disease (ESRD), which occurs mainly in hemodialysis (HD) patients, are especially vulnerable to severe COVID-19 due to the older age and high frequency of comorbidities, such as diabetes mellitus (DM) and hypertension in this population [1-4].

Compared to the general population, chronic HD patients have a higher incidence of COVID-19 infection due to impaired B- and T-lymphocyte functions, susceptibility to molecular immunosuppression, and systemic inflammation caused by uremia [5-7]. The presence of comorbid diseases and immunosuppression in patients with kidney transplantation complicate the management of COVID-19 infection in this group of patients. This may be due to the suppression or aggravation of symptoms by immunosuppression, and from the underlying disease [8].

In this prospective study, we examined the demographic, clinical, laboratory, and radiological results of all HD and kidney transplant (KT) patients

diagnosed with COVID-19 infection between 11th March 2020 and 11th March 2021.

Methodology

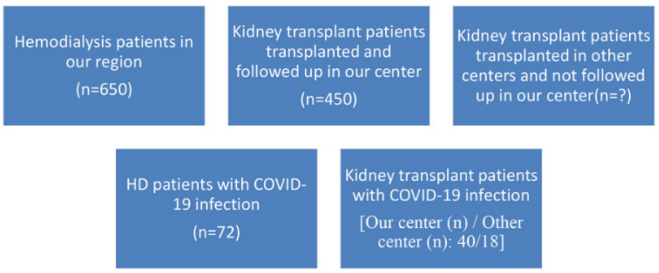
Study Design and Participants

Polymerase chain reaction (PCR) positive COVID-19 HD and KT patients admitted to our hospital were included in this single-center prospective study. The present study was approved by the institutional Ethics Board of the Health Minister and our hospital with number 577 and 579. The study protocol conforms to the Declaration of Helsinki [9]. Informed consent was waived due to the urgent need to collect data during COVID-19. Data of KT and HD patients with COVID-19 were collected from the hospital data system by the relevant transplant surgeon and nephrologist. The clinical status of the patients was followed up with the clinician working in the COVID clinic.

Our hospital has operated as a COVID hospital since 11th March 2020. As of this date, the kidney transplant program was temporarily suspended until March 2021. However, ambulatory service for follow-ups of transplant patients continued. Treatment of patients was arranged and prescribed through teleconferencing as far as possible.

There are 450 kidney transplantation patients that followed up in our hospital. These patients can also consult the physicians in our transplant center if they experience any symptoms related to COVID-19 infection. However, there are also transplant patients in our city and neighboring provinces who are not followed up by our organ transplant center. These patients prefer to follow up at centers in other cities where they have undergone a kidney transplant, and we do not have data on their numbers. In addition, first-year cases where immunosuppression was taken most intensively due to the interruption of kidney transplantation in the first year of the COVID-19 were excluded from this study.

Figure 1. Distribution of patients (The number of patients with kidney transplant transplanted in other centers and not followed in our center is not available).



There are five dialysis centers serving 650 patients with HD in our region. Patients with HD diagnosed with COVID-19 were referred to our hospital (Figure 1).

Except for the patients with a positive PCR test from external centers (an external center is one that is far off from the patient's residence, so these patients were not followed up in our center) and who were referred to us, PCR test for SARS-CoV-2 has been performed for all patients admitted to our hospital with fever, dyspnea, cough, loss of smell/taste, abdominal pain, diarrhea, nausea, vomiting, muscle pain, fatigue, and arthralgia. All the patients with suggestive symptoms of COVID-19 were also evaluated with a chest computerized tomography (CT). The presence of ground-glass opacities, crazy-paving patterns, and consolidation areas was defined as findings consistent with COVID-19. Patients with the above-mentioned findings but whose COVID-19 diagnosis was not confirmed by repeated PCR tests and outpatients were excluded from this study.

Patients' drug and other therapy

Patients' intensive care needs, oxygen needs, mechanical ventilation status, mask oxygen needs and Continuous Positive Airway Pressure (CPAP) needs were evaluated. Hydroxychloroquine, favipiravir, dexamethasone, and antibiotherapy for secondary infection or prophylaxis were used in medical treatment. Worsening symptoms, laboratory results, such as dramatic elevation in C-reactive protein (CRP), ferritin and D-dimer levels, and lung involvement in CT, were regarded as hospitalization indications. Transplant patients with COVID-19 were treated in a specialized clinic for patients with COVID-19 outside of the transplant unit. Treatment was arranged by clinicians in the COVID-19 clinic with the consultation of a nephrologist and transplant surgeon. Immunosuppresors, such as calcineurin inhibitors (tacrolimus and cyclosporine), anti-metabolite agents (mycophenolate mofetil, mycophenolic acid), and steroids, were revised. First, antimetabolite agents were discontinued. Steroid dose (prednisolone) was doubled (from 5 mg/day to 10 mg/day). Inflammation parameters (CRP, procalcitonin), kidney function tests, and immunosuppressors were closely monitored. Immunosuppressors except for steroids were discontinued in patients unresponsive to treatment.

Demographic and laboratory data

Demographic data (age, sex) of the patients, stage of chronic kidney disease (CKD), co-morbid status (if any) (coronary heart disease, congestive heart failure,

DM, hypertension, malignancy, asthma, and chronic obstructive pulmonary disease) were obtained from the hospital database and dialysis/transplant centers' records. Also, hemogram (white blood cell, neutrophil, lymphocyte, platelet), CRP, D-dimer, procalcitonin, biochemical values, namely aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine kinase (CK), lactate dehydrogenase (LDH), sodium, potassium, glucose, urea, and creatinine), electrocardiogram (ECG) and troponin were measured according to the clinical conditions of the patients.

Statistical analysis

All statistical analyses were performed using the IBM SPSS software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Continuous variables were presented as a median and interquartile range, whereas categorical variables were presented as counts and percentages. The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Continuous variables were compared using Student's *t*-test or Mann-Whitney U test according to the data distribution. Categorical variables were compared with chi-square or Fisher's

Table 1. Demographic and clinical characteristics of the hemodialysis patients.

Characteristics	All patient (n = 72)	Dead (n = 15/20.8%)	Discharged (n = 57/79.2%)	*p* value
Age	57.5 (43-65)	72 (63-79)	54 (40-62)	**< 0.001**
Female	36 (50%)	11 (73.3%)	25 (43.9%)	**0.042**
Etiology of ESKD				
Diabetic nephropathy	31 (43.8%)	11 (73.3%)	20 (35.1%)	0.08
Hypertensive kidney disease	34 (47.2%)	4 (26.7%)	27 (47.4%)	0.96
Glomerulonephritis	2 (2.8%)	0	2 (3.5%)	0.46
ADPCKD	4 (5.6%)	0	4 (7%)	0.29
Urologic abnormality	3 (3.2%)	0	3 (5.2%)	0.46
Hemodialysis Access				
AVF	52 (72.2%)	14 (93.3%)	35 (66.7%)	**0.04**
Temporary catheter	9 (12.5%)	0	9 (15.8%)	0.10
Tunneled catheter	11 (15.2%)	1 (6.7%)	10 (17.5%)	0.29
Dialysis time (month)	39 (10-94.5)	81 (34-107)	33 (9-83.5)	0.07
Symptom of admission: n (%)				
Fever	23 (31.9%)	4 (26.7%)	19 (33.3%)	0.62
Cough	14 (19.4%)	3 (20%)	11 (19.3%)	0.95
Dyspnea	26 (36.1%)	12 (80%)	14 (24.6%)	**< 0.001**
Myalgia or arthralgia	14 (19.4%)	5 (33.3%)	9 (15.8%)	0.46
Diarrhea	2 (2.8%)	0	2 (3.5%)	0.46
Laboratory findings median (Q1-Q3)				
Leukocyte count (× 1000/mm³)	7.86 (4.93-9.67)	7.73 (4.61-10.7)	8.04 (4.96-9.67)	0.96
Lymphocyte count (× 1000/mm³)	0.89 (0.65-1.16)	0.79 (0.46-1.16)	0.91 (0.69-1.17)	0.25
Hemoglobin (g/dL)	10.9 (9.3-11.9)	11 (9.6-11.4)	10.9 (9.3-11.9)	0.77
Thrombocyte count (× 1000/mm³)	197 (144-233)	188 (124-245)	200 (148-257)	0.72
Albumin (g/L)	3 (2.8-3.3)	2.9 (2.5-3)	3.1 (2.8-3.4)	**0.004**
ALT (U/L)	13.5 (13-29)	11 (6-25)	14 (18-20.5)	0.55
Creatinin kinase (IU/L)	79.5 (38.5-141.2)	133 (60-348)	69 (37-130)	0.068
LDH (U/L)	288 (232-401)	290 (241-512)	288 (227-373)	0.24
CRP (mg/L)	56 (20.2-114.7)	115 (93-210)	43 (15-100)	0.061
D-Dimer (Ug/L)	489 (298-996)	896 (569-1864)	426 (283-832)	**0.006**
Procalcitonin (ng/mL)	0.8 (0.28-2.98)	4.6 (1.81-12.1)	0.6 (0.21-1.30)	**< 0.001**
Ferritin (ng/mL)	920 (449-1778)	790 (460-1160)	841 (416-1591)	**0.018**
Treatments used for Covid-19 n (%)				
Hydroxychloroquine	20 (27.8%)	3 (20%)	17 (27.8%)	0.45
Favipiravir	60 (83.3%)	14 (93.3%)	46 (80.7%)	0.24
Dexamethazon	20 (27.8%)	6 (40%)	14 (24.6%)	0.23
Admitted to hospital, n (%)	49 (68.1%)	13 (92.9%)	36 (62.1%)	**0.028**
Length of hospital stay (LOS) [(days, median (Q1-Q3)]	9 (5-14)	10 (5-17)	10 (5-13)	0.839
ICU admission n (%)	16 (22.2%)	12 (85.7%)	4 (6.9%)	**< 0.001**
MV in ICU, n (%)	10 (13.9%)	9 (64.3%)	1 (1.7)	**< 0.001**

AVF: Arteriovenous fistula; ESKD: End stage kidney disease; HTKD: Hypertensive kidney disease; ADPCKD: Autosomal dominant polycystic kidney disease; WBC: White blood cell; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CRP: C-reactive protein; MV: Mechanical ventilation; ICU: Intensive care unit.

exact tests whenever appropriate. Evaluation of survival in univariate analyses was performed with the log-rank test. Significant results in univariate analysis were analyzed using Cox regression analysis. The effect size was adjusted for all variables with a univariate significance level of $p < 0.05$. Adjusted hazard ratios (HR), along with their 95% CIs were presented. A *p*-value of < 0.05 was considered statistically significant.

Results

Patients with HD

Following the decision taken by the provincial health authority, HD patients diagnosed with laboratory-confirmed COVID-19 in the five dialysis centers in the city between 11th March 2020 and 11th March 2021 were included in the present study. We enrolled 72 patients, 36 (50%) female and 36 (50%) male. The median age was 57.5 (43-65) years. The mean dialysis treatment period of the patients was 39 months (10-94.5). All the patients underwent thorax CT. Pulmonary findings were not observed in two of them. The most common abnormalities in thorax CT findings (87.9% of the patients) were ground-glass appearance and irregular opacities. Lesions affected the lungs bilaterally in 83.3% of the patients. No statistical significance was found between the groups concerning the frequency of ground glass appearance and bilateral lung involvement.

The most common presenting symptoms were dyspnea (36.1%), followed by fever (31.9%), cough (19.4%), and fatigue/malaise (19.4%). Only a few patients complained of sore throat (2.8%).

The most common primary causes of ESRD in these patients were hypertensive kidney disease (47.2%) and diabetic nephropathy (43.1%), followed by polycystic kidney disease (5.6%), focal segmental glomerulosclerosis (2.8%), vesicoureteral reflux (2.8%) and in one patient, nephrolithiasis (1.4%).

Coexisting comorbidities were hypertension (75%), DM (43.1%), coronary artery disease (29.2%), two patients had asthma, one patient had a previous cerebrovascular accident and one patient had a history of malignancy.

Almost all of our patients were receiving HD treatment three times a week before being diagnosed with COVID-19. Most patients (72.2%) were dialyzed using arteriovenous fistula or non-tunneled hemodialysis catheter (12.5%)/tunneled dialysis catheters (15.3%).

White blood cell, lymphocyte, platelet counts, and hemoglobin, as well as CRP, procalcitonin, D-dimer, ferritin, ALT, LDH, and CK tests, were reviewed in both outpatient and hospitalized patients (Table 1).

The rate of patients taking hydroxychloroquine was 27.8%, and the rate of those who took favipiravir was 83.3%. In 48 patients, anti-biotherapy was started because of a secondary infection or its prophylaxis (66.7%). Also, dexamethasone was administered in 20 (27.8%) patients.

Among our 72 patients, 48 (66.6%) patients who needed oxygen therapy or had low oxygen saturation and moderate or poor general condition were hospitalized. Sixteen (26.3%) of these 48 patients were admitted to the intensive care unit. Ten (13.9%) patients were intubated and connected to a mechanical ventilation device. Nasal oxygen support was sufficient for the rest of the patients hospitalized in the clinic. The median length of stay for the inpatients was nine (5-14) days, and the median length of stay in the intensive care unit (ICU) was five days (2-11). Fifteen of our patients (20.8%) died.

All patients were divided into two groups according to the presence and absence of in-hospital mortality. The groups were compared according to demographic, clinical, laboratory findings, and COVID-19 treatments.

Table 2. Cox regression model for the analysis of independent variables associated with death.

Characteristic	*p* value	HR (95% CI for HR)		
Age	0.010	1.070	1.016	1.126
DM	0.147	2.537	0.721	8.924
Dyspnea	0.099	0.296	0.069	1.259
Hemoglobin	0.708	1.114	0.633	1.960
Leukocyte	0.438	1.0	1.0	1.0
Ferritin	0.432	1.0	0.999	1.002
D-Dimer	0.851	1.0	0.999	1.001
Albumin	0.297	0.898	0.735	1.099
CRP	0.855	1.001	0.994	1.007
Procalcitonin	0.969	0.999	0.966	1.034

CRP: C-reactive protein; DM: Diabetes mellitus.

Table 3. Demographic and clinical characteristics of kidney transplant patients.

Characteristic	All patients n = 58	Dead n = 9 (15.5%)	Discharged n = 49 (84.5%)	*p* value
Age	43.67 (18-75)	46.3 (18-66)	43.18 (18-75)	0.58
Gender, n (%)				
Female	21 (36.2%)	1 (11.1%)	20 (40.8%)	0.135
Male	37 (63.8%)	8 (88.9%)	29 (59.2%)	
Coexisting disorder				
Diabetes mellitus	21 (36.2%)	9 (100%)	12 (24.5%)	**< 0.001**
Hypertension	23 (39.7%)	4 (44.4%)	19 (38.7%)	-
Ischemic heart disease	39 (67.2%)	8 (88.9%)	31 (63.3%)	0.247
Heart failure	8 (13.8%)	2 (22.2%)	6 (12.2%)	0.597
Chronic viral hepatitis	3 (5.2%)	1 (11.1%)	2 (4.1%)	0.403
Epilepsy	1 (1.7%)	0 (0%)	1 (2%)	-
AHUS	1 (1.7%)	1 (11.1%)	0 (0%)	-
Primary kidney disease				
Diabetic nephropathy	20 (34.5%)	3 (33.3%)	17 (29.3%)	-
Hypertension	18 (31%)	2 (22.2%)	16 (32.6%)	-
Urologic disease	7 (12%)	0 (0%)	7 (14.3%)	-
CGN	2 (3.4%)	0 (0%)	2 (4.1%)	-
ADPCKD	2 (3.4%)	0 (0%)	2 (4.1%)	-
PGD	4 (6.9%)	0 (0%)	3 (6.1%)	-
Other	5 (8.6%)	4 (44.4%)	22 (44.9%)	-
Immunsuppressive drugs				
Tac + MMF/MFA + P	48 (82.8%)	7 (77.8%)	41 (83.7%)	-
Cs + MMF/MFA + P	5 (8.6%)	0 (0%)	5 (10.2%)	-
Eve + MMF/MFA + P	2 (3.4%)	1(11.1%)	1 (2%)	-
Tac + Eve + P	1 (1.7%)	0 (0%)	1 (2%)	-
Eve + P	1 (1.7%)	1(11.1%)	0 (0%)	-
Tac + Azo + P	1 (1.7%)	0 (0%)	1 (2%)	-
Laboratory findings median (Q1-Q3)				
CRP (mg/L)	36 (13.7-97.5)	185 (122-219)	28 (12-71)	**< 0.001**
Normal	9 (15.5%)	0 (0%)	9 (18.4%)	-
(× of upper normal value)				
1-5	15 (25.9%)	0 (0%)	15 (30.6%)	-
5-10	14 (24.1%)	1(11.1%)	13 (26.5%)	-
10-20	16 (27.6%)	5 (55.6%)	11 (22.4%)	-
> 20	4 (6.9%)	3 (33.3%)	1 (2%)	-
Creatinine	1.23 (1-1.58)	1.8 (0.98-4.17)	1.2 (0.99-1.51)	0.061
Urea	40 (31-53)	153 (45-236)	39 (29-51)	**0.001**
Leukocyte count (× 1000/mm³)	7.05 (4.5-8.9)	12.6 (5.4-16.2)	7 (4.2-8.6)	**0.025**
Lymphocyte count (× 1000/mm³)	0.9 (0.58-1.6)	0.6 (0.23-0.75)	1 (0.63-1.65)	**0.004**
Thrombocyte count (× 1000/mm³)	199 (157-222)	159 (89-217)	201 (165-228)	0.159
ALT (U/L)	24 (14-40)	24 (14-79)	24 (14-39)	0.675
AST (U/L)	27 (20-46)	81 (25-117)	26 (19-37)	**0.018**
LDH (U/L)	338 (248-420)	556 (461-1122)	288 (224-350)	**< 0.001**
Procalcitonin (ng/mL)	0.24 (1.1-2.4)	4.3(0.12-10.2)	0.19 (1.09-1.1)	**0.012**
Ferritin (ng/mL)	426 (206-1026)	1133 (499-2638)	267 (193-817)	**0.007**
D-Dimer (Ug/L)	432 (217-1537)	2172 (900-6525)	286 (180-637)	**< 0.001**
Hemoglobin (g/dL), mean ± SD	11.7±2.21	9.6 ±1.64	12.1±2.08	**0.001**
Anemia (< 10g/dL)	11(19%)	4 (44.4%)	7 (14.3%)	0.056
Leukopaenia (< 4000)	11 (19%)	1 (11.1%)	10 (20.4%)	1
Lymphopenia (< 1500)	41 (70.7%)	9 (100%)	32 (65.3%)	**0.047**
Thrombocytopenia (< 150 × 10³)	13 (22.4%)	4 (44.4%)	9 (18.4%)	0.102
Symptoms on admision, n (%)				
Fever	23 (39.7%)	6 (66.7%)	17 (34.7%)	0.135
Cough	25 (43.1%)	7 (77.8%)	18 (36.7%)	**0.031**
Dyspnea	16 (27.6%)	7 (77.8%)	9 (18.4%)	**0.001**
Myalgia or arthralgia	37 (63.8%)	4 (44.4%)	33 (67.3%)	0.262
Diarrhea	11 (19%)	0 (0%)	11 (22.4%)	0.184
Headache	14 (24.1%)	2 (22.2%)	12 (24.5%)	1
Loss of smell	10 (17.2%)	0 (0%)	10 (20.4%)	0.335
Covid-19 PCR test positivity	54 (93.1%)	8 (88.9%)	46 (93.9%)	0.501
CT findings				
No findings	18 (31%)	0 (0%)	18 (36.7%)	**0.045**
Unilateral involvement	4 (6.9%)	0 (0%)	4 (8.2%)	1
Bilateral minimal involvement	7 (12.1%)	0 (0%)	7 (14.3%)	0.581
Bilateral middle involvement	13 (22.4%)	2 (22.2%)	11 (22.4%)	1
Bilateral diffuse involvement	16 (27.6%)	7 (77.8%)	9 (18.4%)	**0.001**
Admitted to hospital, n (%)	40 (69%)	9 (100%)	31 (63.3%)	**0.045**
Length of hospital stay [(days, median (Q1-Q3)]	10 (6-14)	11 (7-17)	8 (5-13)	**0.013**
Time from symptoms onset to admission [days, (Q1-Q3)]	3 (2-5)	4 (3.5-6.5)	2 (2-5)	**0.012**
ICU admission, n (%)	10 (17.2%)	8 (88.9%)	2 (4.1%)	**< 0.001**
MV in ICU, n (%)	8 (13.8%)	8 (88.9%)	0 (0%)	**< 0.001**
Covid-19 drug treatments, n (%)				
Hydroxychloroquine	7 (12.1%)	2 (22.2%)	5 (10.2%)	0.296
LMWH	50 (86.2%)	9 (100%)	41 (83.7%)	0.334
Favipiravir	50 (86.2%)	9 (100%)	41 (83.7%)	0.334
Prednisolone / metilprednisolone	58 (100%)	9 (100%)	49 (100%)	-
IVIG	2 (3.4%)	0 (0%)	2 (4.1%)	1
Tocilizumab	3 (5.2%)	2 (22.2%)	1 (2%)	**0.06**
Center of tx, n (%)				
Our center	40 (69%)	3 (33.3%)	37 (75.5%)	**0.02**
Other	18 (31%)	6 (66.7%)	12 (24.5%)	

CGN: chronic glomerulonephritis; ADPCDK: autosomal dominant polycystic kidney disease; PGD: primary glomerular disease; Tac: tacrolimus; MMF/MFA: mycophenolate mofetil / mycophenolate sodium; P: prednisolone; Eve: everolimus; CS: cyclosporine; Azo: azothiropurine; MV: Mechanical ventilation; ICU: Intensive care unit; LMWH: Low Molecular Weight Heparin; IVIG: intravenous imminoglobuline; AHUS: Atypical Hemolytic Uremic Syndrome.

Between the two groups, increased age, female gender, arteriovenous fistula (AVF) as the access route to dialysis, dyspnea as an admission symptom, increased D-dimer and decreased albumin, ferritin was statistically significant in the presence of the in-hospital mortality group (Table 1).

There was no significant relationship between the two groups regarding the comorbid disease, white blood cell, lymphocyte, platelet count, procalcitonin, CRP, ALT, and CK values (Table 1).

Age, DM, presence of dyspnea, hemoglobin, albumin, CRP, ferritin, leukocyte count, procalcitonin, D-dimer, and procalcitonin were significant in the univariate analysis of 30-day survival in HD patients. However, only age was significant in Cox regression analysis [Hazard ratio (HR) 95% CI 1.070 (19,016-1,126)] (Table 2).

Patients with KT

Fifty-eight KT patients with COVID-19 infection (female, n = 21 (36.2%); male, n = 37 (63.8%)) were included in this study. The median age was 44.5 years (28.7-55.2). The median time between the time of transplantation and diagnosis of COVID-19 infection was 71 months (25-140). Fifty-four (93.1%) of patients were PCR-confirmed. Laboratory and imaging findings of the other four patients were compatible with COVID-19. There were no CT findings in 18 (31%) patients. The most common CT findings were bilateral ground-glass appearance and diffuse opacities. The most common symptoms were myalgia and arthralgia (n = 37, 63.8%)

The most common cause of kidney failure was diabetic nephropathy (n = 20, 34.5%). The most common accompanying disease was hypertension (n = 39, 67.2%). One of our patients was being treated with Eculuzimab due to atypical hemolytic syndrome (AHUS) postoperatively (Table 3).

The rate of use of hydroxychloroquine was 12.1%. Most patients were treated with favipiravir (n = 50, 86.2%) and low molecular weight heparin (LMWH). Antibiotics were administered in 41 (70.7%) patients for prophylaxis or treatment of a secondary infection. The meantime of hospitalization was 10 days (6-14). Ten patients (17.2%) were treated in the intensive care unit. Nine (22.5%) of the hospitalized patients died. The median time between the onset of symptoms and admission to the hospital was three (2-5) days. This rate was two (2-3) and five (4-5.75) days, respectively, for patients followed up at our center or the external centers ($p < 0.001$). In addition, hospitalization rates of these patients were 60% (n: 24/40) and 89 % (n: 16/18), respectively ($p = 0.034$). Although age, DM, CRP, urea, leukocyte count, shortness of breath, ferritin, bilateral involvement in CT images, and follow-ups of patients from external centers were significant in the univariate analysis of survival in KT patients, no variables were significant in the Cox regression analysis.

The mortality rate was 20.8% (15/72) and 15.5% (9/58) in the HD and KT groups, respectively. There was no statistically significant difference between the patients with HD and KT concerning mortality (p = 646).

Discussion

This study aimed to share our experience with KT and HD patients since 11th March 2020, when the first case of COVID-19 was observed in Turkey. The mortality rate was high in both patients with HD and KT, as expected [2,3,10]. However, there were studies claiming that mortality in solid organ transplantation (SOT) cases is not different from other patients. Rinaldi *et al.* in their study, including 885 (24 SOT and 861 non-SOT) patients, found 30-day mortality in SOT and non-SOT cases, respectively, 19% (n = 4) and 22.1% (n = 186) [11]. However, in their study, the mean age of patients was lower than in our study.

Four groups were included in a multicentric retrospective and observational study in which 47 centers in Turkey participated with 1,210 patients: control (n = 450), HD (n = 390), KT (n = 81), and stage 3-5 CKD patients (n = 289). The mortality rate was 4%, 16.2%, 11.1%, and 28.4% in control, HD, KT, and CKD groups, respectively. Although the mortality was statistically higher in HD and CKD groups than the control group, there was no difference between the KT and control groups [12]. The mortality rate in our study was 20.8% (15/72) and 15.5% (9/58) in the HD and KT groups, respectively. This difference was not statistically significant ($p = 0.646$). However, in the KT group, the patients were younger ($p = 0.001$), and none of the transplant cases had a post-transplant time < 12 months. One of the reasons for the high mortality in transplant cases may be the immunosuppression used. However, there was no control group in our study.

Villanego *et al.* in their study divided patients into four groups according to posttransplant KT age and post-transplant time in their study: age < 65 years and posttransplant time > 6 months, age < 65 and time ≤ 6, age ≥ 65 and time > 6 and age ≥ 65 and time ≤ 6; and the mortality rate was 11.3%, 24.5%, 35.4%, and 54.5%, respectively. The first six months of intensive immunosuppression following the transplant and age > 65 years were predictors for mortality in this study [13].

One of the interesting data in our study is that mortality was lower in univariate analysis in KT cases whose post-transplant outpatient follow-up was performed in our center ($p = 0.02$). The mortality rate was 7.5% (n: 3) out of 40 patients treated in our center. One of these patients, who had a history of coronary artery disease without obvious involvement in the lung, died of myocardial infarction. It was suspected that it might be a myocardial infarction caused by COVID-19 infection [14]. The low mortality in cases followed up by our center may be due to close contact with the patients by a transplant doctor and earlier admission to the hospital. However, this was not significant in Cox regression analyses. In addition, the symptoms, laboratory findings, and imaging of the patients who were not hospitalized were followed up in the COVID-19 outpatient clinic.

Alberici *et al.* evaluated 20 transplant patients admitted to the hospital in their study. The mean time between the onset of symptoms and admission to the hospital was 5.5 (3.3-8) days. All immunosuppressions of the patients, except steroids, were discontinued after hospitalization. Five (25%) patients died. HD was performed on one of the patients [15]. In our study, forty KT patients were hospitalized. The mean time between the onset of symptoms and admission to the hospital was three (2-5) days. The mortality rate was 22.5% in hospitalized patients. There was a significant difference between the patients followed up in our center and patients followed up in external centers concerning the time before the admission to the hospital. It was two (2-3) and five (4-5.75) days, and the mortality rate was 7.5% and 33.3%, respectively. One of our patients was taken to the HD program due to worsening graft functions.

A total of 1,073 cases were included in the present study in which European Renal Association COVID-19 Database (ERACODA) data were evaluated. There were 305 (28%) patients with KT and 768 (72%) patients with HD, and mortality was 21% and 25%, respectively. The mean age was 60 ± 13 and 67 ± 14 years, respectively. Advanced age was related to mortality in the patients with KT. Fragility and advanced age were related to mortality in patients with HD [16]. Mortality in patients with HD was associated only with age. On the other hand, no mortality-related factor was observed in the Cox regression analysis in patients with KT. The mortality rate in our HD patients group was 20.8%. In other studies on HD patients with COVID-19 infection, mortality rates range from 10% to 31% [4.17]. Our results are consistent with these studies. The overall mortality rate of COVID-19 in the general population has been reported at approximately 3.2% [18]. Hence, although the data are limited, the studies on patients with HD strongly suggest that the mortality rate is much higher in these patients. The presence of comorbid diseases accompanied by chronic renal failure patients and immunosuppression caused by uremia are likely to be contributors to this higher mortality rate.

The main risk factor for in-hospital mortality due to COVID-19 is advanced age. In patients with comorbidities, such as CKD, hypertension, chronic obstructive pulmonary disease, DM, malignancy, obesity, and advanced age, these were the strongest predictor of a poor outcome [19]. In our study, the mean age of HD patients was 57.5 median (43-65) years. The ratio of females to males in our study was 1:1. In the in-hospital mortality group, the mean age was 72 median (63-79) years. In Cox regression analysis, advanced age was statistically significant in 30-day mortality. A meta-analysis included 19 articles and 39 case reports; D-dimer (2-fold), CRP (7-fold), and procalcitonin (2-fold) values were observed in patients with severe disease compared to those with mild forms; it has been shown that high erythrocyte sedimentation rate (ESR) and CRP values are predictive for sepsis and mortality, and lymphopenia and high LDH values are significantly associated with ICU admission [20]. In the HD-specific COVID-19 studies, the mortality rate has been reported to be related to lymphopenia, elevated CRP, dialysis treatment length, elevated D-dimer, and cardiovascular comorbidities so far [21-23]. In our study, we did not find a statistically significant relationship between in-hospital mortality and the predictors mentioned above, but advanced age was more common in the mortality group. The small sample size is likely to limit the significance of our statistical results. Therefore, it is necessary to clarify the clinical course of COVID-19 infection and predictors determining the need for intensive care and mortality in patients with hemodialysis, a group of patients with comorbid diseases frequently.

Limitations

Although this study is prospective, the limitations of our study are the inability to include patients in the first year after transplantation due to the absence of a control group and the cessation of operations.

Conclusions

In conclusion, our findings showed that age is a determinant of mortality in HD patients [Hazard ratio (HR) 95% CI 1.070 (19.016-1.126)]. We did not find a

significant difference in laboratory values between the patients who survived and died. However, none of the variables alone had an effect on mortality in patients with KT. COVID-19 infection is a risk factor for patients with RT and HD. This study was conducted before the vaccination program. Since both HD and KT patients are immunosuppressed, on-time contact with the nephrologist and/or transplant surgeon and admission to the hospital in case of doubt for COVID-19 infection and inclusion of transplant patients in the vaccination programs can reduce the mortality. However, further large-scale prospective randomized studies should be conducted.

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Conflict of interests: No conflict of interests is declared.