

Analysis of COVID 19 Infection in Chronic Kidney Disease and Kidney Transplant Patients in Pandemic Hospital: What Has the Last Year Taught Us?

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Abstract

Objective: This study aims to investigate the mortality factors in hemodialysis patients and kidney transplant patients with COVID-19 patients. **Method:** The demographic, clinic, laboratory, and radiologic signs of the kidney transplant and hemodialysis patients diagnosed with COVID-19 between 11 March 2020-11 March 2021 were evaluated. **Results:** To this study, 72 hemodialysis (median age, 57.5 Q1-Q3:43-65; female:36/50%) and 58 kidney transplant (median age, 44.5 Q1-Q3:28.75-55.25; female:21/36.2%) were included. Fifteen HD patients (20.8%) died. To identify the independent predictors of in-hospital mortality, multivariable logistic regression analyses were performed using the variables in the univariate analyses including age, female gender, diabetes mellitus, ferritin, d-dimer, albumin, CRP, procalcitonin, dyspnea. Age (OR:1.12, 95% [CI]: 1.03-1.21, p=0.004), and dyspnea (OR: 9.7 95% CI 1.80-52.2, p=0.008) were found to be associated with in-hospital mortality. Nine (15.5%) of transplant patients died. The median time from the beginning of symptoms to the time of admission was 3 days (2-5). And this rate was 2 (2-3) and 5 (4-5.75) days, respectively, for patients followed up in our center and the external centers (p<0.001). Although an increase in CRP, ferritin, D-dimer levels, dyspnea, and bilateral involvement in CT images was statistically significant in the univariate analysis, no single factor was found to be related to mortality in multivariate analysis. **Conclusion:** Both HD and renal transplant patients should be followed closely. Early admission of HD and RT patients might be life-saving when suspected. Early inclusion of these patients into the vaccination program might reduce mortality. However, large-scale prospective randomized studies are needed.

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Fifteen HD patients (20.8%) died. To identify the independent predictors of in-hospital mortality, multivariable logistic regression analyses were performed using the variables in the univariate analyses including age, female gender, diabetes mellitus, ferritin, d-dimer, albumin, CRP, procalcitonin, dyspnea. Age (OR:1.12,

95% [CI]: 1.03-1.21, $p=0.004$), and dyspnea (OR: 9,7 95% CI 1.80-52.2, $p=0.008$) were found to be associated with in-hospital mortality.

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Conclusion: Both HD and renal transplant patients should be followed closely. Early admission of HD and RT patients might be life-saving when suspected. Early inclusion of these patients into the vaccination program might reduce mortality. However, large-scale prospective randomized studies are needed.

Keywords:

What is already known about this topic?

The increase in mortality due to covid 19 in organ transplant patients has been reported in the literature.

What does this article add?

The close interaction between the patients and clinicians might be lifesaving and reduce the mortality in patients with COVID-19 infection especially in the transplant patients.

Introduction:

At the end of 2019, a novel coronavirus (ie, 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 throughout most countries of the world. SARS-CoV-2 disease (COVID-19) primarily manifests as respiratory tract infection with symptoms ranging from those of a mild upper respiratory infection to severe pneumonia, acute respiratory distress syndrome, and death. COVID-19 disproportionately affects patients with pre-existing comorbidities, such as patients with various types of kidney disease.

The Chinese Center for Disease Control and Prevention published data of 44,672 COVID-19 patients. The mortality rate was 2.3% in this study. This rate was 1.3%, 3.6%, 8% and 14.8% between the ages of 50-59, 60-69, 70-79, >80 years respectively. The main risk factors for mortality were cardiovascular diseases (10.5% mortality), diabetes mellitus (7.3%), chronic lung disease (6.3%), hypertension (6%), and cancer (5.6%).

Patients with end-stage kidney disease (ESKD) that occurs mostly from hemodialysis patients are particularly vulnerable to severe COVID-19 due to the older age and high frequency of comorbidities, such as diabetes and hypertension in this population. (1-4)

The currently known mode of transmission of Covid-19 is the droplet route. Compared to the general population, chronic hemodialysis 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 disease and the use of immunosuppression in patients with kidney transplantation complicate the management of COVID-19 in this group of patients. This may be due to the suppression or aggravation of symptoms by immunosuppression, as well as from the underlying disease.(8)

In this study, we examined the demographic, clinical, laboratory, and radiological results of all hemodialysis and kidney transplant patients diagnosed with laboratory or radiological confirmed COVID-19 between 11 March 2020 and 11 March 2021.

Materials And Method:

Between 11 March 2020 – 11 March 2021, PCR positive COVID-19 hemodialysis patients from five dialysis centers, including our center which is a pandemic hemodialysis center as a result of the decision taken by

provincial health authorities were included in the study. There were 650 hemodialysis patients in these five dialysis centers.

Additionally, there are 450 patients with kidney transplantation followed up in the organ transplant center of our hospital. These patients can also consult the physicians in our transplant center in the presence of 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 be followed up in centers in other cities where they were transplanted, and we do not have data on their numbers.

Except for the patients whose PCR test is positive from external centers and referred to us; in our hospital PCR for SARS-CoV-2 has been performed in all patients admitted with fever, dyspnea, cough, loss of smell/taste, abdominal pain diarrhea, nausea, vomiting, muscle pain, fatigue, arthralgia with the nasopharyngeal and oropharyngeal specimens. All the patients with suggestive symptoms of COVID-19 were also evaluated with chest computerized tomography. The presence of ground-glass opacities, crazy-paving patterns, and consolidation areas was defined as the findings consistent with COVID-19 disease. Patients with the above-mentioned findings but whose Covid-19 diagnosis was not confirmed by repeated PCR tests and outpatients were not included in the study.

Dialysis Therapy:

After being assigned by the health authorities of our city, a unit with 5 hemodialysis devices and a separate water system was created in a separate isolated area in our hospital for covid-19 hemodialysis patients. It was planned to perform dialysis treatments in this unit for mobile patients with good general conditions. Dialysis treatment of patients in the intensive care unit who received invasive or non-invasive oxygen support was planned with bedside dialysis devices with a mobile water system. Patients whose general condition was moderate or poor and who needed oxygen support were hospitalized. Dialysis treatments of patients who did not have an indication for hospitalization and who were given outpatient treatments were planned in an isolated area prepared for Covid-19 patients.

Patients Drug And Other Therapy:

Patients' intensive care needs, oxygen needs, and mechanical ventilation status, mask oxygen needs and CPAP needs were evaluated. Hydroxychloroquine, favipiravir, dexamethasone, and antibiotherapy for secondary infection or prophylaxis were used in medical treatment. Worsening in symptoms, laboratory results such as dramatic elevation in CRP, ferritin and D-dimer levels and lung involment in CT were regarded as an indication for hospitalization. Transplant patients with COVID-19 patients were treated in a specific clinic for COVID-19 patients outside of transplant unit. Treatment was arranged by clinicians in COVID-19 clinic with the consultation to nephrologist and transplant surgeon. Immunosuppresors such as calcineurin inhibitors, anti-metabolite agents, and steroids were revised. Steroid dose (Prednisolone) was doubled (from 5 mg/day to 10 mg/day). Inflammation parameters (CRP, procalcitonine), kidney function tests and immunosuppresors were closely monitored. Immunosuppresors except to steroid were discontinued in the unresponsive patients to treatment.

Demographic And Laboratory Information:

The demographic information (age, sex) of the patients, stage 5 CKD etiology, co-morbid status (if any) (coronary heart disease, congestive heart failure, diabetes mellitus, hypertension, malignancy, asthma, chronic obstructive pulmonary disease) were obtained from the hospital database and dialysis/transplant centers' records. Also, hemogram (White blood cell, neutrophil, lymphocyte, platelet), C-reactive protein (CRP), d-dimer, procalcitonin, biochemical values (AST, ALT, creatinine kinase, LDH, sodium, potassium, glucose, urea, creatinine), electrocardiogram (ECG) and troponin were measured according to clinical conditions of patients

Ethics Board And Helsinki Declaration:

This study was approved by the institutional ethics board of the Health Minister and our hospital. The study protocol conforms to the Declaration of Helsinki.(9)

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 median and interquartile range, whereas categorical variables as count and percentages. The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Continuous variables were compared with Student's t-test or Mann-Whitney U test according to the distribution of the data. Categorical variables were compared with chi-square or Fisher's exact tests whenever appropriate. Univariate and multivariate logistic regression analyses were conducted to assess the association in the hospital mortality. In stepwise multivariate regression analysis (Backward, Wald), the effect size was adjusted for all variables with a univariate significance level of <0.05 . Adjusted odds ratios (OR), along with their 95% CIs were presented. A 2-tailed p-value of <0.05 was considered statistically significant.

Results:

Result For Hemodialysis Patients

As a result of the decision taken by the provincial health authority, patients who were diagnosed with laboratory-confirmed Covid -19 hemodialysis in 5 dialysis centers in the city center between 11 March and 11 March 2021 were included in the study. We included 72 patients, 36 (%50) were female and 36 (%50) were 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 of the patients had positive RT-PCR. All the patients had thorax computerized tomography (CT). Pulmonary findings were not observed in two patients on thorax CT. The most common abnormalities as thorax CT findings in 87.9% of the patients were ground-glass appearance and irregular opacities. Lesions often affected the bilateral lungs in 83.3% of the patients. No statistical significance was found between the groups in terms of frequency of ground glass appearance and bilateral lung involvement.

The most common presenting symptom overall was dyspnea (36.1%) followed by fever (31.9%), cough (19.4%), and fatigue/malaise (19.4%). Patient less commonly reported sore throat (2.8%).

The most common primary causes of ESKD in these patients were hypertensive kidney disease (47.2%) and diabetic nephropathy (43.1%) and 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%), diabetes mellitus (%43.1), coronary artery disease (%29.2), two patients had asthma, 1 patient had a previous CVA and 1 patient had a history of malignancy.

Almost all of our patients were receiving hemodialysis treatment 3 times a week before being diagnosed with COVID-19. Most patients (72.2%) dialyzed via arteriovenous fistula or non-tunneled hemodialysis catheter (12.5%) / tunneled dialysis catheters (15.3%).

The white blood cell, lymphocyte, hemoglobin, platelet counts as well as CRP, procalcitonin, d-dimer, ferritin, ALT, LDH, creatinine kinase tests were reviewed in all of our patients who were treated both in outpatient and hospitalized patients. A comparison of blood tests of alive and deceased patients is available in Table 1 with their averages.

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 for secondary infection or prophylaxis (66.7%). Also, dexamethasone was administered in 20 (27.8%) patients.

Of our 72 patients, 48 (66.6%) who needed oxygen therapy or had low oxygen saturation and moderate or poor general condition were hospitalized. Sixteen (26.3%) of 48 patients were admitted to the intensive care unit. Ten (13.9%) of the patients hospitalized in the intensive care unit were intubated and connected to a

mechanical ventilation device. Nasal oxygen support was sufficient for the patients hospitalized in the clinic. The median length of stay of the inpatients was found to be 9.5 (5-13), and the median length of stay in the intensive care unit was 4.5 (1.25-10.75). 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.

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

There was no significant relationship between the two groups in terms of comorbid disease, White blood cell, lymphocyte, platelet, procalcitonin, CRP, ALT, CK, values. (Table 1)

To identify the independent predictors of in-hospital mortality, multivariable logistic regression analyses with a stepwise backward model were performed using the variables in the univariate analyses including age, female gender, diabetes mellitus, ferritin, d-dimer, albumin, CRP, procalcitonin, dyspnea. Age (OR:1.12, 95% confidence interval [CI]: 1.03-1.21, $p=0.004$), and dyspnea (OR: 9.7 95% CI 1.80-52.2, $p=0.008$) were found to be associated with in-hospital mortality. (Table 2)

Result of the Transplant Patients

Our hospital was accepted as a pandemic hospital after March 11, 2020, following the first case of COVID-19 seen in our country. As of this date, the kidney transplant program was temporarily suspended until March 2021. Ambulatory service for follow-ups of transplant patients was continued. Treatments of patients were arranged and prescribed through the teleconference method as far as possible. Fifty-eight transplant (female: 21/36.2%; Male:37/63.8%) patients with COVID-19 infection were included. The median age was 44.5 years (28.7-55.2). 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 4 patients were compatible with COVID-19 infection. There were no findings in the 18 (31%) patients in the imaging. The most common CT findings were bilateral ground-glass findings and diffuse opacities. The most common symptom was myalgia and arthralgia (n:37/63.8%).

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

The rate of use of the hydroxychloroquine was 12.1%. Most of the patients were treated with favipiravir (50/86.2%) and Low Molecular Weight Heparin (LMWH). Antibiotics were administered in the 41 (70.7%) patients for profilaxia or due to seconder infection. Mean time of hospitalization was 10 days (6-14). Ten patients (17.2%) were treated in the intensive care unit. Nine (22.5%) of hospitalized patients died. The median time between the onset of symptoms and admission to the hospital was 3 (2-5) days. And this rate was 2 (2-3) and 5 (4-5.75) days, respectively, for patients followed up in our center and the external centers ($p<0.001$). In addition, the hospitalization rates of these patients were 60% (n: 24/40) and 89% (n: 16/18), respectively ($p: 0.034$).

There was no statistically significant difference between the kidney transplant and hemodialysis patients in terms of mortality. Nonetheless, mortality rate was high among the young patients in the transplant group ($p:0.001$). In addition, first-year cases where immunosuppression was taken most intensively due to the interruption of kidney transplantation in the first year of the pandemic were not included in the study.

Discussion:

This study aims to share our experiences in transplant and hemodialysis patients since the time 11 March 2020 when the first case of COVID-19 was observed. The mortality rate was found to be high in both HD and kidney transplant patients as expected.(2,3,10) However, there are also studies claiming that mortality in solid organ transplantation (SOT) cases is not different from other patients. Rinaldi et al. in their study

including 885 (SOT: 24, non-SOT: 861) patients, they found 30-day mortality in SOT and non-SOT cases, respectively, 19% (n: 4) and 22.1% (n: 186).(11) However, in this study, the mean age of patients was lower than in our study.

Four groups were included in the multicentric retrospective and observational study in which 47 centers in Turkey participated with 1210 patients: control (n: 450), HD (n: 390), RT (n: 81), and stage 3-5 chronic kidney patients (CKD, n: 289). The mortality rate was 4%, 16.2%, 11.1% and 28.4% in the control, HD, RT, and CKD groups respectively. Although the mortality was statistically higher in HD and CKD groups compared to the control group. There was no difference between the RT and control groups.(12) There was no control group in our study. And the mortality rate was found to be 20.8% (15/72) and 15.5% (9/58) in the HD and RT groups respectively. This difference was not statistically significant. (p:646). However, in the RT group, the patients were younger (p: 0.001) and none of the transplant cases had a post-transplant time <6 months.

Villanego et al. in their study divided patients into four groups according to posttransplant RT 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 of our study is that mortality was found to be lower in univariate analyzes in RT 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 myocardial infarction (MI) caused by a COVID-19 infection.(14) The low mortality in cases followed up by our center may be due to close contact with the patients by transplant doctor and earlier admission to the hospital. In addition, the symptoms, laboratory findings, and imaging of the patients who were not hospitalized were followed.

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%) of the patients died. Hemodialysis was performed on a patient.(15) Forty patients were hospitalized in our study. The mean time between the onset of symptoms and admission to the hospital was 3 (2-5) days. The mortality rate was %22.5 in the hospitalized patients. There was a significant difference between the patients followed up in our center and patients followed up in external centers in terms of the time before the admission to the hospital. It was 2 (2-3) and 5 (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.

1073 cases were included in the study in which European Renal Association COVID-19 Database (ERA-CODA) data were evaluated. There were 305 (28%) RT patients and 768 (72%) HD patients and mortality was 21% and 25% respectively. The mean age was 60±13 ve 67±14 years respectively. The advanced age was found to be related to mortality in the RT patients. And fragility and advanced age were found to be related to mortality in HD patients.(16) Although an increase in CRP, ferritin, D-dimer levels, lymphopenia, dyspnea, and bilateral involvement in CT images was statistically significant in the univariate analysis, no single factor was found to be related to mortality in multivariate analysis.

The mortality rate in our patient HD group was 20.8%. In other studies on hemodialysis 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 by about 3.2%.(18) Hence, although the data are limited, the studies on HD patients 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 in due to COVID-19 is advanced age. In patients with co-

morbidities such as chronic kidney disease, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, malignancy, and obesity, advanced age was the strongest predictor of a poor outcome under infectious diseases.(19) In our study, the mean age of HD patients was 57.5 median (43-65) years. Half of our patients were women and half were men. In the in-hospital mortality group, the mean age was found to be 72 medians (63-79) years. Multivariable logistic regression analysis was showed that advanced age and dyspnea as admission symptoms were statistically significant associated with in-hospital 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 c-reactive protein (CRP) values are predictive for sepsis and mortality, and lymphopenia and high LDH values are significantly associated with intensive care unit(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 and dyspnea (possibly result of hypoxemia) were more common in the in-hospital 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 hemodialysis patients, which are a group of patients with comorbid diseases frequently.

Limitations:

Limitations in our study are to be retrospective and absence of a control group and the inability of including post-transplant first-year patients due to a halt in operations.

Conclusion:

In conclusion, we found that, unlike previous hemodialysis studies, age and the presence of dyspnea as the complaint of presentation are determinants of in-hospital mortality in our study. We did not find a significant difference in laboratory values between the patients who survived and died. COVID-19 infection is a risk factor for RT and HD patients. This study was conducted before the vaccination program. Since both HD and RT 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 to the vaccination programs can reduce the mortality. However, large-scale prospective randomized studies are needed.

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