10.5152/turkjnephrol.2022.21234

Review

Turkish Journal of Nephrology

Recommendations for Kidney Patients in COVID-19 Era Based on Current Evidence

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ABSTRACT

Patients with chronic kidney disease, patients on dialysis, and kidney transplant recipients are at high risk of mortality and morbidity due to coronavirus disease-19. Most patients with chronic kidney disease are elderly and have other comorbidities. In addition, some of these patients have been exposed to immunosuppressive drugs to treat their underlying primary disease or to prevent allograft rejection. This general profile of chronic kidney disease patients renders them susceptible to a more severe course of coronavirus disease-19 once they are infected with severe acute respiratory syndrome coronavirus 2. Many studies showed that impaired kidney function on admission is an independent risk factor for a more severe course of coronavirus disease-19 with significantly increased risk for hospital and intensive care unit admission, intubation, mechanical ventilation, and death. Coronavirus disease-19 vaccination is crucial to create immunity in the general community, but the evidence addressing this specific population is scarce. However, based on the current evidence, all patients with chronic kidney disease are strongly recommended to receive the available vaccine in their country against coronavirus disease-19, and booster doses will presumably prove necessary for this group of patients. Furthermore, vigilant use of protective measures is strongly recommended for this patient population. Current studies and recommendations from health authorities should be followed closely.

Keywords: Clinical nephrology, COVID-19, hemodialysis, peritoneum dialysis, kidney transplantation

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Received: December 21, 2021 **Accepted:** December 29, 2021

Cite this article as: Öztürk S, Velioğlu A, Tuğlular S. Recommendations for kidney patients in COVID-19 era based on current evidence. *Turk J Nephrol.* 2022;31(1):7-16.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic affected more than 260 million people in 215 countries resulting in more than 5.3 million deaths and nearly 90 000 intensive care unit (ICU) admissions all around the world.[1] Data, experience, and scientific knowledge from all affected countries revealed that patients with chronic kidney disease (CKD), patients on dialysis, kidney transplant (KT) recipients, and patients on immunosuppressive therapy for other reasons are at high risk of mortality and morbidity due to coronavirus disease-19 (COVID-19). The very rapid evaluation of data collected through various studies led to statements and recommendations for managing these kidney patients calling the nephrologists and the health authorities to action.[2] Indeed, this patient population is one of the most vulnerable groups when faced with COVID-19 since most have multiple comorbidities. Furthermore, the increasing global burden of CKD has already become a worldwide public health problem with approximately 850 million patients worldwide. Since the start of the pandemic, the major development in fighting COVID-19 has been the very rapid launch of vaccines. Herein, as we reach the end of the second year and fourth wave of the pandemic, we aimed to review the current state of recommendations for the prevention, management, and short- and long-term consequences of COVID-19 among kidney patients.

PATIENTS WITH KIDNEY DISEASE, NOT ON KIDNEY REPLACEMENT THERAPY

Most patients with CKD also have other comorbidities, including diabetes and cardiovascular disease. In addition, some of these patients have been exposed to immunosuppressive drugs to treat their underlying primary disease and are mostly elderly. This general profile of CKD patients renders them susceptible to a more severe course of COVID-19 once they are infected with SARS-CoV-2. For example, in a recently published study by De Lusignan et al[3] addressing risk factors for COVID-19, among 3802 patients, 32.9% of 207 patients with CKD tested positive for COVID-19 while only 14.4% of the 3595 individuals without CKD tested positive (odds ratio (OR) 1.91 [95% CI 1.31-2.78]).

Indeed, the data collected demonstrated that CKD is also an important risk factor for mortality as well as morbidity. Data from OpenSafely Project revealed that the dialysis and transplant population and CKD patients have a much higher mortality risk for COVID-19.[4] The relative adjusted hazard ratios (HRs) were 3.69, 3.53, and 2.52 for dialysis, transplantation, and CKD patients, respectively. CKD risk was higher than diabetes and/or chronic heart disease. Recently, Gibertoni et al[5] reported that the increase in mortality risk correlated with the stage of CKD. In their study population from Italy, the incidence of COVID-19 in CKD patients was 4.09%, while it was 0.46%in the general population. They reported the crude mortality rate as 44.6% in CKD patients with COVID-19.

According to The International Health Outcome Predictive Evaluation for COVID-19 registry (HOPE-COVID-19), CKD prevalence was 8.5% among infected individuals. Furthermore, patients with impaired kidney function on admission had a higher incidence of complications like sepsis and respiratory failure. Moreover, lower estimated glomerular filtration rate (eGFR) on admission was an independent risk factor for in-hospital mortality with a 2-fold increase of death for eGFR 30-60 mL/min/1.73 m^2 and a 5-fold increase in mortality risk when eGFR was <30 mL/min/1.73 m^2.[6]

Furthermore, depending on the severity, COVID-19 may result in an acute-on-chronic kidney injury and further impair their underlying kidney function necessitating kidney replacement therapy during this infection. Not only a higher incidence of acute kidney injury (AKI) among patients with elevated baseline creatinine on admission due to COVID-19 was reported but also this subgroup had a higher prevalence of ICU admission.[7] Cheng et al[7] concluded that previous chronic kidney impairment might have a negative impact on the clinical evolution and fatality risk of COVID-19.

In a prospective cohort study from Spain, which included 1821 patients, 43.5% with elevated creatinine on admission had underlying CKD. The reported raw mortality rate was higher in patients with a previous history of CKD (41.1%) than patients with normal serum creatinine on admission (5.8%).[8]

In the nationwide retrospective case–control study including 219 961 individuals from Korea, where the effect of underlying comorbidities on the infection and comorbidities of COVID-19 was addressed, Ji et al[9] reported that CKD and end-stage kidney disease (ESKD) resulted in severe COVID-19. In another study where the patient characteristics and outcomes of 11 721 patients with COVID-19 hospitalized across the United States were addressed, 4.3% of the study population had CKD. In the latter study, Fried et al[10] also reported an increased risk of severe COVID-19 requiring mechanical ventilation (OR = 1.22) and mortality (OR = 1.66) associated with CKD. Similar data were reported from Mexico, where the epidemiological data on the increased risk of hospitalization and death in patients with COVID-19 and pre-existing non-communicable diseases (NCD) and modifiable risk factors were analyzed. Among the NCD, pre-existing CKD increased the risk of death most (OR = 2.31) compared to diabetes, immunosuppression, obesity, hypertension, and chronic obstructive lung disease.[11] Severe COVID-19 requiring hospitalization (HR = 2.54), ICU admission (HR = 1.12), intubation (HR = 1.30), and mortality (HR = 2.31) were associated with CKD. Data from OpenSafely revealed that among the CKD patients [6.8% of the cohort (17 278 392 people)], mortality increased as eGFR decreased: HR 1.33 (1.28-1.40) for eGFR 30-60 mL/min/1.73 m^2 versus HR 2.52 (2.33-2.72) for eGFR <30 mL/min/1.73m^2.[3]

The studies above and others have clearly demonstrated that underlying CKD is an independent risk factor for a more severe course of COVID-19 with significantly increased risk for hospital and ICU admission, intubation, mechanical ventilation, and

MAIN POINTS

- Underlying chronic kidney disease (CKD) is an independent risk factor for a more severe course of coronavirus disease-19 (COVID-19) infection with significantly increased risk for hospital and intensive care unit admission, intubation, mechanical ventilation, and death.
- Evaluation of kidney function and previous CKD history must be a priority during the initial presentation of patients with COVID-19.
- Coronavirus disease-19 may also have an impact on the increasing number of CKD patients worldwide.
- Kidney function follow-up should be an integral part of post-COVID management in the latter group of patients.
- All patients with kidney disease, including patients with CKD stages 1-5 not on dialysis, patients on dialysis, and kidney transplant (KT) recipients are at an increased risk of severe COVID-19, increased mortality, and morbidity.
- All patients with kidney disease, including patients with CKD stages 1-5 not on dialysis, patients on dialysis, and KT recipients should be vaccinated against severe acute respiratory syndrome coronavirus 2.
- Due to low antibody response in all CKD patients, health care workers, patients, and their household members should continue safety measures, including using masks and keeping social distance.

death. These data suggest that evaluation of kidney function and previous CKD history must be prioritized during the initial presentation of patients with COVID-19.

Although data on the kidney outcome of patients who developed AKI during COVID-19 are scarce, about 20-35% of these patients have only partial kidney recovery, and some—although few—remained dialysis-dependent.[12]

Post-COVID-19 syndrome has been defined as occurring in 10-35% of patients[13] who seemingly recovered from COVID-19 characterized by symptoms including fatigue, cognitive disturbances, dyspnea, chest pain, arthralgia, and a decrease in quality of life.[14] Huang et al[15] reported that among the long-term health consequences of COVID-19, an important issue was the loss of kidney function defined as eGFR <90 mL/min/1.73 m^2. Among patients who did not have AKI during COVID-19, 13% had decreased eGFR at 6 months, while when all participants were included, 35% had decreased e-GFR by 6 months. Therefore, COVID 19 may also impact the increasing number of CKD patients worldwide; kidney function follow-up should be an integral part of post-COVID management in the latter group of patients.

Determining health policy for COVID-19 vaccination is crucial to create immunity in the general community to prevent severe illness in COVID-19. Unfortunately, the representation of CKD patients in currently available phase 3 trials is low. Impaired innate and adaptive immunity is common in CKD patients. Furthermore, uremic milieu, older age, and erythropoietin and vitamin D deficiency depending on CKD stages may also decrease the immunologic response to vaccines.[16] Therefore, in CKD patients from stages 3 to 5, not on immunosuppressive treatment, the efficacy of vaccines may be lower. Currently, the evidence addressing this specific population is scarce. Moreover, the variety of vaccines available across the world makes it difficult to deduce a conclusion. To date, there are 4 types of vaccines classified according to the structure: mRNA-based vaccines (Moderna and Pfizer-BioNTech), vaccines utilizing replication-deficient viral vectors (Oxford-AstraZeneca, Johnson and Johnson, and Sputnik V), inactivated virus (Sinopharm, Sinovac, and Coronavac), and protein subunits (Novavax). In Turkey, 2 vaccines are available: mRNA vaccine (Pfizer-BioNTech) and inactivated virus (Sinovac and CoronaVac). However, most current data about vaccination in patients with CKD, patients on dialysis, and KT patients come from the BNT162b2 vaccine. Based on the current evidence, all CKD patients are strongly recommended to receive the available vaccine in their country against COVID-19, and booster doses will presumably prove necessary for this group of patients.

CAN RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM INHIBITORS BE SAFELY USED IN PATIENTS WITH COVID-19?

Another important issue raised during the COVID-19 pandemic was the concern about using medications acting on the renin–angiotensin–aldosterone system (RAAS), especially in patients with COVID-19. The reason for this concern was that the SARS-CoV-2 virus invaded the cells through the angiotensin-converting enzyme 2 (ACE2) receptor. The major idea behind this concern was the possibility of increased virulence and infectivity having a negative impact on the prognosis. Several studies, however, failed to show any association of either COVID-19 or a worse prognosis and RAAS inhibitors.[17-19] Recently, data from the European Renal Association COVID-19 Database (ERACODA) did not reveal any significant association between previous use or continuation of RAS blockade among patients on dialysis and KT recipients with COVID-19 severity.[20] Since RAAS inhibitors are extensively used for hypertension, cardiovascular diseases, and nephrology practice, it is not recommended to stop these medications before, during, or after the COVID-19.[19] Furthermore, the possibility of using ACE2 receptor as a therapeutic target is currently under investigation.[21-24]

PATIENTS ON KIDNEY REPLACEMENT THERAPY

Hemodialysis

Like many other CKD patient groups, hemodialysis (HD) patients are at high risk for short-term negative consequences of COVID-19 such as hospitalization, need for intensive care support, and mortality. In the multicenter data reported from Turkey, the in-hospital mortality rate was 16.3%, and the ICU admission rate was 23.6% in patients undergoing HD, and adjusted mortality and adjusted combined ICU admission and/or mortality outcomes in HD group were significantly higher than the control group [HR (95% CI): 2.32 (1.21-4.46); $P = .011$].[25,26] The European Renal Association COVID-19 Database data showed that the 28-day mortality attributable to COVID-19, calculated using historical control data matched with propensity score, was 20.0% in 3285 HD patients undergoing dialysis.[27] New York, United States, data showed 28% in-hospital mortality among HD patients.[28] Different mortality rates were reported from different parts of the world.[29] Moreover, COVID-19 risk is significantly higher in in-center HD than dialysis methods at home, namely peritoneal dialysis (PD) and home HD.

On the other hand, COVID-19-related symptoms, inflammatory biomarkers, and abnormalities in chest radiographs may persist into the late post-COVID periods.[30-32] Although many studies describe clinical sequelae in COVID-19 survivors in the general population, there are few studies on the same topic in CKD or HD patients.[33] In addition, post-COVID complications and survival of the patients have not been published extensively among HD patients.

Och et al[34] including 79 HD patients discharged from hospital [median age of 70.0 (64.0-76.5)], reported at least 1 persistent symptom in 93.7% and 81% of the patients post-COVID third and sixth month, respectively. Fatigue or muscle weakness (60.76% and 47.04%), palpitations (40.51% and 30.14%), and dyspnea (43.03% and 34.25) were the most common symptoms. They

also showed a decrease in the quality of life, mainly in the pain/discomfort and anxiety issues. Lung-scan abnormalities have been reported in 63% of patients and dyspnea in 16% 4 months after discharge in a general population cohort.[32] Some important recommendations for dialysis centers for preventing and controlling COVID-19 by the Turkish Ministry of Health guidelines were summarized in Table 1.

Turkish Society of Nephrology conducted an observational study on COVID-19 survivors with CKD and compared it with similar CKD patients without COVID-19. HD group in this study[35] included 1223 patients (635 COVID-19 positive HD group, 588 COVID-19 negative control HD group). The patients' baseline demographics, comorbidities, medicines, HD characteristics, and baseline laboratory tests were almost similar between the groups. The 28th day mortality and mortality between 28th day and 90th day were higher in the COVID-19 HD group than the control HD group [19 (3.0%) patients vs. none (0%); 15 (2.4%) patients vs. 4 (0.7%) patients, respectively]. 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. The presence of respiratory symptoms, rehospitalization, need for home oxygen therapy, lower respiratory tract infection, and A-V fistula thrombosis were significantly higher in the COVID-19 group in both the first 28 days and between 28 and 90 days. Adjusted 90-day mortality of COVID-19 HD group was

Table 1. Basic Recommendations in the Turkish Ministry of Health Guidelines for Preventing and Controlling Infections in Dialysis Centers[37]

Patients and their relatives

- They should be repeatedly informed about COVID-19 symptoms and prevention methods.
- Posters containing this information should be kept in visible locations of the center.

Medical personnel

- Medical personnel should wear masks during all times in the dialysis center and be questioned every day for signs and symptoms of COVID-19.
- When a health care worker at the center is diagnosed with COVID-19, other personnel management should be planned according to a specific algorithm.

Precautions should be taken before patients arrive at the dialysis center

- All patients and their relatives who come to dialysis should be wearing masks.
- Public transport should not be used to and from the dialysis center.
- Patients who have the possibility should be encouraged to come to the center by private vehicle.
- Patients with fever and respiratory symptoms should be encouraged to call the dialysis center to report them beforehand.
- When the patients arrive at the center, the symptoms of COVID-19 should be questioned before entering the treatment unit.
- Waiting areas floor and surfaces should be cleaned and disinfected frequently and regularly.
- Cleaning and disinfection of the machine and the area should be done immediately after a patient with COVID-19 leaves the dialysis unit.

Dialysis procedure

- Whether the patients have symptoms compatible with COVID-19 or not, each dialysis station should have at least a 1-m distance.
- Patients should wear a mask throughout the dialysis process.
- Eating should be avoided during dialysis. However, patients can bring simple foods such as sugar to prevent hypoglycemia.

During the dialysis procedure of COVID-19 patients

- These patients should undergo dialysis in a separate room with a closed door if possible.
- If it is not possible, a distance of at least 1 m in all directions should be maintained between symptomatic patients and other patients during the procedure. If a separate room is unavailable, the patient should be treated in a far corner.
- If there is more than 1 COVID-19 patient, they can be grouped, and if possible, it should be ensured that the same health care worker serves in the same session.
- Isolation rooms reserved for hepatitis B patients should only be used for HBsAg-positive patients with symptoms of COVID-19.

Ventilation, Cleaning, and Disinfection

- Rooms should be ventilated frequently by opening windows.
- Fans and air conditioners should not be used.
- Central ventilation systems should be arranged to provide fresh air circulation. Maintenance of ventilation systems and filter changes should be done regularly.
- After each dialysis session, the units should be cleaned and disinfected regardless of whether the patient has a diagnosis of COVID-19.
- Cleaning and disinfection should be concentrated on places that are touched frequently by hand (light switches, door handles, etc.).
- The health care worker caring for all patients should take standard contact and droplet isolation precautions.
- Gloves, aprons, medical masks, and disposable face protectors should be disposed of in the medical waste bin.
- Non-disposable material (glasses and face protectors) can be disinfected and reused with 70% alcohol.
- Multi-use textile aprons can be washed and reused.

COVID-19, coronavirus disease-19.

significantly higher than the control HD group [HR (95% CI): 7.258 (2.538-20.751)].

A similar high prevalence of shortness of breath was reported in the general population after the COVID-19 period. Halpin et al[36] showed that breathing difficulty assessed 4 to 8 weeks after hospital discharge was a significantly higher symptom among patients discharged from ICU than the ward group (65.6% in ICU group vs. 42.6% in ward group). All this may indicate ongoing pulmonary inflammation with pulmonary sequelae of COVID-19 patients.

The possible post-COVID problems among HD patients are presented in Table 2.

Table 2. Possible Problems in HD Patients at Post-COVID Period[25,26,32,34,40-45]

General issues
Decrease in the quality of life
Pain/discomfort and anxiety
Fatigue or muscle weakness and palpitations
Hypercoagulation condition
Increased A-V fistula thrombosis and other arterial or venous thromboses
Catheter-related thrombosis
Microvascular and macrovascular thrombosis
Respiratory system problems
Persistent symptoms, such as dyspnea or coughing
Need for home oxygen therapy
Lower respiratory tract infection
Abnormalities in chest radiographs
Biochemical issues
Decreased serum albumin and hemoglobin
High inflammation markers, such as C-reactive protein, ferritin
Survival, rehospitalization
Increased mortality and need for intensive care support
Rehospitalization need
Unanswered issues related to COVID-19 vaccination
Is the mRNA vaccine response in HD patients diminished and/or delayed?
Does the response rate differ in HD patients with or without pre-existing COVID-19?
How long will neutralizing antibodies persist after immunization?
How protective is the vaccine-derived immunity?
Does responses to inactivated and mRNA vaccines different?

COVID-19, coronavirus disease-19; HD, hemodialysis.

Since there is no evidence that routine anticoagulation strategies should be different in HD patients who have had COVID-19, continuing routine anticoagulation and following patients closely for possible thrombotic processes looks like the most suitable strategy.

Another post-COVID challenge is the potential unanswered problems associated with COVID-19 vaccination. Initial clinical trials of COVID-19 did not include patients on dialysis. On the other hand, the response of HD patients who have had COVID-19 to the mRNA vaccine seems similar to those not on dialysis.[38,39] However, the antibody response in HD patients without pre-existing COVID-19 occurs with a delay.[36] On the other hand, critical questions such as whether patients on dialysis will develop SARS-CoV-2 antibodies as reliably as healthy adults, how long neutralizing antibodies will persist after immunization, and how protective the vaccine-derived immunity is have not yet been fully answered.[39]

As a result, many problems remain in maintenance HD patients who have had COVID-19. Especially, mortality and respiratory problems, rehospitalization, vascular access problems, and coagulation were increased. More careful follow-up of maintenance HD patients is required in the post-COVID-19 period, therefore, long follow-up studies are needed. On the other hand, although there are potential issues to be resolved with the COVID-19 vaccine, we suggest vaccination of HD patients with or without pre-existing COVID-19. How many doses, what kind of vaccines will be preferred, the application of the additional reminder dose, and the dose intervals are mostly recommended by the health authorities in the countries and by the relevant scientific societies. For this reason, current scientific evidence-based updates on these issues should be followed (Table 3).

Table 3. Recommendations for Kidney Transplant Recipients

- All KT recipients should be vaccinated against SARS-CoV-2.
- KT recipients with prior COVID 19 should receive a vaccine.
- The third dose of vaccine to KT recipients who have previously received 2 doses can increase antibody response to SARS-CoV-2.
- Vaccination should be performed prior to transplantation (ideally a minimum of 2 weeks before transplant).
- Vaccine dose should be delayed at least 1-3 months after transplantation or anti-rejection therapies (for patients treated with specific B-cell depletion agents such as rituximab may require a more extended period).
- Changing the immunosuppressive regimen before vaccination is not currently recommended.
- To date, SARS-CoV-2 vaccines are safe and well-tolerated with no evidence of an increased risk of rejection attributable to the vaccine.
- Vaccination is also recommended for donors and household members of the KT recipients.

KT, kidney transplant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Peritoneal Dialysis Patients

PD has become a priority in incidental ESKD patients due to the possibility of individual treatment at home and the lower risk of COVID-19 transmission during the pandemic.[46] In a study that includes historical trends from Medicare and Medicaid data, the initialization rate of PD (against HD) was 24% higher.[47] However, almost all studies on COVID-19 outcomes are related to HD patients and included early results. Studies of PD patients in the active phase of COVID-19 or the post-COVID-19 period are scarce. In a study by Jiang et al[48] from Wuhan, China, only 8 of 818 patients on PD reported being diagnosed with COVID-19. In the aforementioned study of ERACODA, 125 of 4298 patients were on PD, the 28-day probability of death was 25.0% in those treated with PD.[49] Only 2 of 59 ESKD patients were on PD in that abovementioned study from New York, United States.[29]

In a national multicenter study, supported by the Turkish Society of Nephrology, the data at the end of the first month of COVID-19 and post-COVID 90 days outcomes were investigated among PD patients with confirmed COVID-19.[25] A control PD group was also created from the same centers with similar characteristics and PD duration. The study included 223 patients (COVID-19 group: 113, control group: 110) from 28 centers. On day 28, serum albumin and hemoglobin levels were significantly lower in the COVID-19 group. Respiratory symptoms, hospitalization, lower respiratory tract infection, PD regimen change, ultrafiltration deficiency, and hypervolemia were significantly higher after 28 days in the COVID-19 group. On the 90th day, there was no significant difference in laboratory parameters. Only 1 patient from the COVID-19 group died between 28 and 90 days. There was no death in the control group. Respiratory symptoms, malnutrition, and hypervolemia were significantly higher at day 90 in the COVID-19 group.

In conclusion, there are not enough studies yet to make definitive suggestions on the post-COVID issues of PD patients. However, the mortality rate after COVID-19 in PD patients may not differ from the control PD group. Moreover, especially respiratory system symptoms may continue to be significant problems.

Kidney Transplantation and Transplant Patients

KT recipients are at an increased risk of severe COVID-19 compared to the general population. The reported rate of mortality ranges between 16.9% and 28% in the early stages of the pandemic.[50-53] In the multicenter study of 109 KT recipients from Turkey, the mortality rate was found to be 12.8%, and this relatively low mortality rate was attributed to the younger patient population.[54] A large multicenter study has noted a higher mortality rate than[53] dialysis population. However, Ozturk et al[26] reported a significantly lower in-hospital mortality rate in KT recipients (11.1%) compared to HD patients (16.2%). Older age (>50 years), recent transplantation, and the presence of comorbidities, including hypertension, diabetes, cardiovascular disease, and obesity, are the well-known risk factors for severe COVID-19 among the KT population.[2,53,55]

During the first wave of the pandemic, most transplant centers suspended transplant activities, the primary underlying reason for which was shifting resources from transplant to care of COVID-19 patients. Transplant activity was continued in some transplant centers only for urgent and low immunological risk patients. Reports from national registries have shown that the number of transplantation significantly decreased in Europe, America, and Asia.[56] Indeed, the Turkish Society of Nephrology Registry showed a 35% decrease in the number of kidney transplantation in 2020 compared to the previous year.[57] After the first wave of the pandemic, many transplant centers have cautiously restarted kidney transplantation activity.

Another consequence of the COVID-19 pandemic in transplant practice was the failure to attend clinical follow-up due to tight adherence to isolation and social distance rules by the patients. Transplant physicians tried to solve this problem through telemedicine visits.

Although management of immunosuppressive treatment decisions was left to individual physicians' clinical experience in early pandemic periods, global transplant communities' recommendations regarding managing immunosuppression in KT recipients with COVID-19 were published about 2 months after the start of the pandemic.[58,59] According to these recommendations, a general consensus was reached to decrease the dose of or eliminate mycophenolate Mofetil (MMF)/mycophenolic acid (MPA) from the immunosuppressive regimen for COVID-19 positive symptomatic patients depending on the disease course. In severe patients, reduced doses of calcineurin inhibitors were also recommended. In the early periods of the pandemic, higher mortality rates reaching up to 30% were reported.[60] A recently published paper from the United States showed decreasing mortality rate in the second wave. This finding was majorly attributed to dexamethasone and remdesivir use in solid organ transplant (SOT) recipients similar to the general population.[61] However, the long-term consequences of COVID-19 in KT recipients remain unclear.

As for many other viral infections, the most critical success in pandemic control is the evolution of SARS-CoV-2 vaccines. Decreasing the risk for symptomatic COVID-19 and reducing viral transmission were expected with widespread vaccination. However, unlike the general population, KT recipients had lower antibody production rates to many vaccines, mainly due to impaired B lymphocyte functions influenced by the immunosuppressive drugs. Indeed, current data have suggested that immune responses to SARS-CoV-2 vaccines are far from optimal, and studies investigating the effectiveness of various SARS-CoV-2 vaccines in transplant populations continue worldwide.[62]

The types of SARS-CoV-2 vaccines have been summarized above. This section will assess the impact of SARS-CoV-2 vaccines on

transplant practice by summarizing the immune response to vaccines, factors affecting vaccine response, the safety of the vaccines, and lastly, recommendations that should be kept in mind while practicing daily transplant routine.

Since none of the SARS-CoV-2 vaccines contain live viral particles, they can all be used safely in KT recipients. KT recipients should be recommended to receive any kind of vaccine available in their countries regarding to local distribution and regulations.

IMMUNE RESPONSE AND EFFICACY OF SARS-COV-2 VACCINES

The majority of published vaccine experiences in KT recipients were on mRNA vaccines. mRNA vaccines, mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) provide a lower seroconversion rate in KT recipients than healthy control groups. Antibody responses to the latter vaccines were reportedly higher in patients with CKD, including those on dialysis compared to the KT recipients.[62] Grupper et al[63] reported that only 37.5% of kidney transplantation patients had a humoral response following mRNA vaccines. Variables associated with lower humoral response were older age, high dose corticosteroid use in the last 12 months, and mycophenolate and belatacept use.[61,63,64] Recently, a preliminary study of cell-mediated immune response to SARS-CoV-2 vaccines has shown that half of the antibody-negative patients had developed positive ELISpot tests.[65] Despite poor antibody response, breakthrough COVID-19 in vaccinated KT recipients was infrequently reported. However, the rate of breakthrough COVID-19 was significantly higher than the general population (0.65% vs. 0.001%, respectively).[66] Indeed, some severe cases of COVID-19 were reported developing after 2 vaccination doses.[67] These data suggest that KT recipients remain at high risk for COVID-19 despite adequate vaccination, and they should continue to apply safety measures, including mask-wearing and social distancing.

Vaccination against COVID-19 was started in late January 2020, prioritizing the patients with SOT among other vulnerable or at increased risk groups in Turkey. Since the only available vaccine in Turkey at that time was an inactive form, all SOT recipients, including the KT recipients, received the inactive vaccine form. In a very recent study by Sadioglu et al,[68] the adequate antibody response was achieved in only 18.8% of the KT patients with inactivated Coronavac vaccine. Currently, an mRNA vaccine (BNT162b2, Pfizer-BioNTech) is also available in Turkey, and the choice of inactive or mRNA vaccine is left to the patient's decision. At least a single dose vaccination in patients who have previously had COVID-19 has also been suggested.

Due to the low antibody response in this patient population even with 2 doses of mRNA vaccines, a study was directed to investigate if a third dose would further increase the antibody response, and indeed, with the administration of the third dose of mRNA vaccine, an increased antibody response was reached among KT recipients.[69] Further decrease in the rate of breakthrough infections is expected with the third dose of vaccine.

Although measurement of the antibody titers for vaccine response evaluation and after COVID-19 has not been generally recommended, checking antibody response after vaccination in SOT recipients could be considered. The protective level of antibody titers is unknown and limits the usefulness of antibody testing. Nevertheless, in a recently published article, the authors proposed a vaccine algorithm directed by antibody testing.[70] According to this article, if the anti-spike antibody level is below 264 BAU/mL after 2 doses of mRNA vaccine or after a single dose of mRNA vaccine in individuals who had a recent COVID-19 and the cellular response is positive, the second dose in those who have previous COVID-19 and the third dose in those who have 2 doses of vaccine could be administered. However, this recommendation has not yet been supported by other studies. Prophylaxis with monoclonal antibodies may be a promising method for patients who do not show any antibody and cellular response after the vaccination.[71]

SAFETY OF SARS-COV-2 VACCINES

Severe reactions after SARS-CoV-2 vaccinations are rare. Most of the reported reactions are local pain, fever, and myalgia, and the type and rate of adverse events have been similar in transplant patients compared to the general population.[72] Regarding previous vaccine experiences in the KT recipients, rejection following vaccination seems to be a significant concern about SARS-CoV-2 vaccines. Based on the study findings published by Ou et al.[73] transplantation rejection was seen in only 1 of the 741 participants. Del Bello et al[74] described cellular rejection developed following the third dose of vaccine in a KT recipient. Although the exact pathogenic mechanism of rejection after vaccination has not been fully understood, this concern has to be weighed against the high morbidity and mortality incidence in KT recipients who develop COVID-19. Early good safety data may help address vaccine hesitancy among transplant recipients.

RECOMMENDATIONS FOR SARS-COV-2 VACCINES IN KT PRACTICE

Pre-transplant SARS-CoV-2 Vaccination

The data about the efficacy of the SARS-CoV-2 vaccine in the waitlisted patients showed that the majority of dialysis patients achieved a sufficient humoral and cellular response.[75] Regarding lower vaccine response in transplant patients, vaccinating waitlisted patients is strongly recommended. This recommendation may also tightly apply to highly sensitized waitlisted patients. For kidney transplantation from living donors, vaccination before transplant surgery is recommended for recipients and donors. The recommended time period between at least 1 vaccine dose and surgery is 2-4 weeks. COVID-19 screening with a

polymerase chain reaction test is still recommended and mandatory before surgery.

Post-transplantation SARS-CoV-2 Vaccination

Many guidelines recommend delaying vaccination at least 1 month from transplant surgery and at least 3 months from the use of anti-thymocyte globulin.[71] Two doses of vaccination should be recommended to all KT recipients. Recently, the third dose of vaccination has been suggested for achieving a better humoral response. However, data for the timing of the third dose are scarce. In the recent studies, a third dose mRNA vaccine applied 2 months after the second dose provided increased antibody titers and cellular immune response in KT patients.[73]

Transplant recipients with prior COVID-19 should also receive vaccination since it will provide additional protection. The optimal timing for vaccination in patients who have had COVID-19 infection is not precise. In the general population, 3 months interval is ideal after infection to vaccination. In KT recipients, vaccination is recommended as soon as possible when the disease symptoms are resolved.

Changing either immunosuppressive drugs or doses is not recommended. In addition, modulation of immunosuppression is not advised because of the potential risk of rejection.

Transplant Recipient with Rejection

There should be a period of 4 weeks after anti-rejection therapy (pulse steroid, anti-thymocyte globin, or plasmapheresis). The significant negative impact of rituximab on serological responses to vaccines has been confirmed in various immunosuppressive patient populations[76] (29). It is recommended that vaccination could be performed 4-5 months after recent use or 2-4 weeks before the rituximab treatment.

Despite these improvements in transplant practice after vaccination, health care workers, KT patients, and their household members should continue safety measures, including using masks and keeping social distance.

The advantages of COVID-19 vaccination on transplant practice can be summarized as follows:

1. Continuation of transplant activities (deceased and living) at full capacity
2. Re-enabling outpatient clinic visits face-to-face and providing regular follow-up
3. Reduction in concerns in the management of maintenance immunosuppressive therapy
4. Possibility of performing full protocol rejection and desensitization treatments

In conclusion, all patients with kidney disease, including patients with CKD stages 1-5 not on dialysis, patients on dialysis, and KT recipients, are at an increased risk of COVID-19-related mortality and morbidity. Based on current evidence, vaccination against SARS-CoV-2 is a universal protection measure and is strongly recommended for this patient population. More studies on these groups are needed to better understand the management and prevention of COVID-19. Therefore, current studies and recommendations from health authorities should be followed closely.

Peer-review: Internally reviewed.

Author Contributions: Concept - S.T.; Design - S.T.; Supervision - S.T.; Literature Search - S.T., S.Ö., A.V.; Writing - S.T., S.Ö., A.V.; Critical Reviews - S.T., S.Ö., A.V.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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