SARS-CoV-2 in Kidney Transplant Recipients

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The COVID-19 pandemic has had a striking impact on kidney transplantation globally. Patients with chronic kidney disease (CKD) and kidney transplant patients are one of the populations most vulnerable to the risks of COVID-19. In the United States alone, there are more than half a million people living with end stage renal disease (ESRD). More than 105,234 kidney transplants were performed in 2019 all over the globe. After the outbreak of COVID-19, all surgeries were stopped as an early response to the pandemic. A drastic fall in the number of kidney transplants was observed, with a fall rate of 59.2% from the 105,234-plus kidney transplants (KTx) in 2019 to 42,948 KTx in 2020.

kidney transplant SARS-CoV-2 COVID-19 Vaccination

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or coronavirus disease 19 (COVID-19), which originated in the city of Wuhan, China, spread worldwide and turned into a global pandemic [1][2]. After the first wave of COVID-19 in March and April of 2020, a second wave of COVID-19 evolved in India, the USA, Brazil, Russia, Spain, and France, with the higher rate of infection and spread [3]. It had infected more than 173 million people and caused more than 3.7 million deaths worldwide as of 8 June 2021 [4]. The third global outbreak of SARS-CoV-2 with the Omicron variant (B.1.1.529) has emerged. The efficiency with which the Omicron variant can spread is high, making it extremely contagious, more so than the original SARS-CoV-2 virus. The transmissibility of the variant is unknown in kidney transplant patients.

The COVID-19 pandemic has had a striking impact on kidney transplantation globally. Patients with chronic kidney disease (CKD) and kidney transplant patients are one of the populations most vulnerable to the risks of COVID-19 [3]. In the United States alone, there are more than half a million people living with end stage renal disease (ESRD) [5].

More than 105,234 kidney transplants were performed in 2019 all over the globe. After the outbreak of COVID-19, all surgeries were stopped as an early response to the pandemic [6]. A drastic fall in the number of kidney transplants was observed, with a fall rate of 59.2% from the 105,234-plus kidney transplants (KTx) in 2019 to 42,948 KTx in 2020 [7].

Transplant and non-transplant nephrologists' practices have been greatly affected by the COVID-19 pandemic. Patients on renal replacement therapy have had to visit the hospital for regular check-ups and in emergencies.

CKD patients on hemodialysis are more susceptible to the rapid spread of the COVID-19 virus due to regular visits to the hemodialysis ward and waiting areas, exposure during transportation, and indirect contact transmission. Transplant evaluation and surgeries were paused as an early response to the pandemic, but dialysis cannot be stopped or paused, unlike transplants [8]. While 80% of the deceased donor kidney transplants in the US were operational, 72% of living donor transplants were fully shut down [9][10].

The published reports and studies suggest that kidney transplant recipients are at an increased risk of severe COVID-19 [11], hospital admissions [12], acute kidney injury [13] and mortality [12][14]. Immunosuppression is a vital part of the post-transplant regimen, which prevents rejection and ensures the longevity of the graft [15][16][17][18]. Due to the decreased T cell immunity in transplant recipients, they are at a high risk of severe bacterial and viral infections, and therefore are at greater risk of mortality from COVID-19 [19].

One OpenSAFELY project analyzed 17 million patients for the factors associated with COVID-19 deaths. This study reported that dialysis, organ transplant and CKD are three of the four comorbidities associated with the highest mortality risk in COVID-19 cases. The risk associated with CKD stages 4 and 5 is higher than that of diabetes mellitus [20]. According to the Global Burden of Disease, an estimated global population of 1.7 billion (22%) is at high risk of severe COVID-19 infection. The CKD risk factor associated with COVID-19 severity was found in 5% of the global population [21]. With the rise of COVID-19 cases and infection, increased stress and anxiety levels are also observed in kidney transplant patients, leading to sleep disturbances and psychiatric disorders, which affect graft function and reduce the required high compliance with transplant regimens [22].

2. Clinical Presentation

The cause of COVID-19 exposure is related to community transmission. The average time between exposure and clinical symptoms is 6–7 days. The most common initial symptoms of COVID-19 in KTx recipients included fever [14][19][23][24][25][26][27][28][29][30][31][32][33][34][35][36] cough [14][19][23][24][25][26][27][28][29][30][31][32][33][34][35], dyspnea [14][19][23][24][25][26][27][28][30][31][32][33][35][36][37] diarrhea [14][19][23][24][25][26][27][30][31][32][34][36][37], myalgia [19][23][24][25][26][28][29][30][32][36] and headache [9][23][25][28][31][34][37]. Other reported symptoms of COVID-19 that were not commonly observed during the first wave of the pandemic were: loss of taste and smell [14][30][31][32][33][37], fatigue [19][23][25][37], emesis [19][25][37], abdominal pain [19][23][32] and throat pain [23][37]. From 42% to 67.9% of the KTx COVID-19 patients reported suffering from acute kidney injury (see **Table 1**) [14][23][31][32][33][36][38][39][40]. Caillard et al. observed 13.2% acute kidney injury (AKI) cases in the non-transplant patient population [31]. Schapiro et al. and Banerjee et al. reported graft loss in 8.5% [40] and 33.3% [38] of the KTx patients due to the COVID-19, respectively. Nearly 10% of the KTx recipients underwent renal replacement therapy [14][31][32][40]. Caillard et al. observed a similar trend in non-transplant patients also, where 10% of the total admitted non-transplant patients underwent renal replacement therapy (RRT) [31].

Table 1. Clinical presentation, treatments and outcomes of COVID-19 in KTx recipients.

Study	Place	Sample Size (N) *	Clinical Presentation #	Treatments #	Immunosuppression Adjustment #	Mortality
Abreshami et al., 2020 [28]	Iran	12	fever, cough, myalgia, headache, shortness of breath, gastrointestinal symptoms	HCQ, LR, AB, Ig	Decrease in MMF/AZT, MMF and CNI	8
Akalin et al., 2020 [26]	USA	36	fever, cough, myalgia, diarrhea, shortness of breath	HCQ, AZ, TL, LL	Withdrawal of F and AMB	10
Azzi et al., 2020 [41]	USA	229	-	HCQ, AB, RD, TL, CP, AK, Ig, LL, SL, AC	Withdrawal of AMB, CNI	47
Banerjee et al., 2020 [38]	UK	7	fever, cough, diarrhea, emesis, shortness of breath	-	Withdrawal of MMF and FK	1
Caillard et al., 2021 [31]	France	273	fever, cough, diarrhea, headache, shortness of breath, loss of smell/taste	HCQ, AZ, LR, OR, TL, RD, AB, AF	Withdrawal of CNI, mTOR, AMB and BC	-
Chavarot et al., 2021 [30]	France	100	fever, cough, myalgia, diarrhea, shortness of breath, loss of smell/taste	HCQ, AZ, TL	Withdrawal of CNI, AMB and BC	26
Coll et al., 2021 [42]	Spain	375		HCQ, AZ, AK, AV	CNI, AMB and mTOR adjustments	103
Cravedi et al., 2020 [36]	USA	144	fever, myalgia, diarrhea, shortness of breath,	HCQ, AB, TL, RD, LR, DC, DR	Withdrawal of FK, MMF	46
Cucchiari et al., 2020 [33]	Spain	28	fever, cough, shortness of breath, gastrointestinal symptoms, loss of smell/taste	HCQ, AZ, LR, TL, Steroids	Withdrawal of MPA/mTOR and CNI	5
Dheir et al., 2021 [39]	Turkey	20	fever, cough, shortness of breath, myalgia, diarrhea	HCQ, FR, DX, ORCP, AB	Withdrawal of AMB, CNI, mTOR	2
Elhadedy et al., 2020 [35]	UK	8	fever, cough, shortness of breath	-	Discontinued MMF, increase/decrease in	No death

Study	Place	Sample Size (N) *	Clinical Presentation #	Treatments #	Immunosuppression Adjustment #	Mortality
					FK	
Elias et al., 2020 [14]	France	66	fever, cough, diarrhea, shortness of breath, loss of smell/taste	HCQ, TL, EL	Withdrawal of MMF/MPA/AZ, CNI	16
Fung et al., 2021 [43]	USA	4	fever, cough, diarrhea, fatigue, shortness of breath	HCQ, LR, TL, AB, RD, CP, Steroids	Withdrawal of MPA, FK, MPA	No death
Gandolfini et al., 2020 [24]	Italy	2	fever, myalgia, diarrhea, shortness of breath	HCQ, AB, LR, DC, RD	Withdrawal of Tac and MMF	1
Giorgakis et al., 2020 [37]	USA	4	fever, cough, loss of smell/taste, emesis, throat pain, fatigue, headache, loss of appetite, rhinorrhea	HCQ, AZ, TL	Decrease in FK, MMF, MPA, CNI	1
Kute et al., 2021 [32]	India	250	fever, cough, myalgia, fatigue, headache, emesis, diarrhea, shortness of breath, gastrointestinal symptoms, loss of smell/taste, throat pain, Z, rhinorrhea, loss of appetite, altered mental state	HCQ, AZ, FR, RD, CP, Ig	Withdrawal of and decrease in AMB, decrease in CNI and increase in PS	29
Mamode et al., 2021 [25]	UK	KTx = 121, W/L = 52	fever, cough, myalgia, fatigue, headache, emesis, diarrhea, shortness of breath,	-	-	KTx-36 W/L-12
Naeem et al., 2020 [44]	USA	3	fever, chills, fatigue, diarrhea, shortness of breath, emesis, gastrointestinal symptoms	CP, CFT, AZ, VM, PT, RD	Withdrawal of MMF, AZT	No deaths
Nair et al., 2020 [19]	USA	10	fever, cough, chills, myalgia, nasal congestion, fatigue, headache, emesis,	HCQ, AZ	Decrease in MPA, MMF and FK	3

Study	Place	Sample Size (N) *	Clinical Presentation #	Treatments #	Immunosuppression Adjustment #	Mortality
			diarrhea, shortness of breath			
Oto et al., 2021 [23]	Turkey	109	fever, cough, myalgia, fatigue, headache, diarrhea, shortness of breath, throat pain	HCQ, OR, LR, FR, GC, TL, AK, AP	-	14
Rinaldi et al., 2020 [27]	Italy	24 (22 KTx)	fever, cough, diarrhea, shortness of breath	HCQ, AZ, DC, TL, Steroids		4 (30 days)
Schapiro et al., 2021 [40]	USA	KTx = 80 W/L = 56	fever, cough, diarrhea, emesis, headache, fatigue, myalgia, shortness of breath,	HCQ, AZ, RD, TL, SX, CP, DY	Withdrawal of, increase or decrease in MMF	KTx = 13 W/L = 19
Shrivastava et al., 2021 [34]	USA	39	fever, cough, diarrhea, headache, altered mental state, hypoxia	HCQ, TL	Withdrawal of or decrease in AMB and CNI	9
Zhang et al., 2020 [29]	China	5	fever, cough, myalgia, fatigue	OR, AB, Ig	Decrease in GC, MMF and CNI	No deaths

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most common location for mucormycosis is the nasal/sinus and orbit, followed by the central nervous system, lungs and bones. Mucormycosis was known to affect patients with kidney-related ailments, even before the pandemic, due to their immunocompromised conditions. The management of patients with COVID-19 infection and conditions relating to existing comorbidities, such as diabetes, altered some of the established causes of mucormycosis in non-immunocompromised patients. However, the kidney transplant patients are still at a higher risk of this disease as a post-COVID-19 complication [45][48][49][50][51][52][53][54][55][56][57].

Sample size of only KTx recipients is mentioned above and not of the controlled group of other transplant patients. # The mentioned symptoms, treatments, immunosuppressive adjustments are not standardized, as each patient experienced different sets of symptoms, based on which each patient was administered medicines and immunosuppressive changes. The above-mentioned "symptoms," "treatments" and "immunosuppression" are mentioned jointly for all the patients. Abbreviations: KTx, kidney transplant; W/L, waiting list. TREATMENTS—AB, antibiotics; AC, anticoagulation; AF, antifungal; AK, anakinra; AP, apheresis; AV, antiretroviral; AZ, azithromycin; CFT, ceftriaxone; CP, convalescent plasma; DC, darunavir-cobicistat; DR, darunavir-ritonavir; DX, dexamethasone; DY, doxycycline; EU, eculizumab; FR, favipiravir; GC, glucocorticoids; HCQ, hydroxychloroquine; Ig, immunoglobulin; IN, ivermectin; LR, lopinavir-ritonavir; OR, oseltamivir; PT, piperacillin; RD, remdesivir; SI, sarilumab; SX, Selinexor; TL, tocilizumab; VM, vancomycin. IMMUNOSUPPRESSIONS—AMB, antimetabolite; AZT, azathioprine; BC, belatacept; CNI, calcineurin inhibitor; PK, tacrolimus; MMF, mycophenolate mofetil; MPA, mycophenolate acid; PS, prednisolone.

3. Treatment and Immunosuppressant Adjustments

There is no standard medicine, treatment or therapy for COVID-19. Different medicines and treatments are administered to the patients mostly based on the clinical symptoms they have. Hydroxychloroquine is used for SARS-CoV-2 patients, for both transplant and non-transplant categories as reported in the majority of the studies [14][19][23][27][30][31][32][33][34][37][42][47]. Azithromycin [19][23][30][31][32][33][37][39][41][47], tocilizumab [14][27][30][31][32][33][36][37][42][47], lopinavir/ritonavir [42][44][58][59][60], darunavir/cobicistat [24][27][36], favipiravir [23][32][39], oseltamivir [23][31][39], antibiotics [19][23][24][31][32][36][39][41][42][43] and strong doses of steroids [27][32][33][36][39] are some of the most prescribed medicines (**Table 1**).

Other administered medicines are macrolides [23][32], antifungal [31], antiretroviral [47], interferon [47], anakinra [23][42][47], corticosteroids [42][47], glucocorticoids [23] and convalescent plasma therapy [44][61]. Intravenous immunoglobulin

therapy [11][42] and convalescent plasma therapy [32][39][41][42] have also been reported as a treatment for moderate to severe COVID-19-infected patients in reported studies.

For the transplant patients suffering from COVID-19, the major dilemma is whether to alter the immunosuppressive regimens that are prescribed to them for the survival of the graft. In the case of continuing with immunosuppressive regimens, the risk of the severity of COVID-19 infection increases, thereby increasing the risk of mortality. Several studies and reports published online describe the treatments followed by them in KTx recipients. The treatment is individualized, and no prescription of standardized treatment or therapy is administered. Many studies and reports reported that doctors scrutinize each patient and, based on the condition, the decision is made to discontinue, withdraw, increase or decrease the immunosuppression [14][19][24][26][30][32][36][37][42][44][47].

Nair et al. reported different types of immunosuppressant adjustments for each patient that were achieved with a decrease in mycophenolate acid, mycophenolate mofetil, sirolimus or mycophenolate mofetil and tacrolimus together [19]. The intake of prednisone was also controlled based on the need of each patient. Elias et al. described the treatment for KTx patients with COVID-19 infection, and the immunosuppressive adjustments varied from patient to patient depending on the need and the intake of medicines [14]. Kute et al., in a multicenter prospective study, described the clinical course of 250 KTx patients, where they reported no change in the steroid dosage in 60% of the patients due to COVID-19 positivity, and also that 28.4% of the patients were put on reduced dosage or discontinued from the calcineurin inhibitor [32]. Further, for the patients suffering from mucormycosis, amphotericin B was given to them and, in severe cases, debridement of the affected tissue was the only available treatment [49][50][51].

4. Mortalities in Kidney Transplant Recipients Due to COVID-19 Infection

According to the French and Spanish registry of ERA-EDTA, the infection rate of COVID-19 was 14 cases per 1000 transplants [62]. The Belgian Society of Nephrology also reported an incidence of 14 cases per 1000 transplants. Patients with a kidney transplant seem to be at a greater risk of severe COVID-19 disease and mortality [63].

Three studies from New York, the United States of America, by Nair et al., Akalin et al. and Schapiro et al. reported a mortality rate of 30% [19], 28% [26] and 52% [40], respectively, among the kidney transplant patients due to COVID-19. The studies from among the European region, including the United Kingdom, Spain, Italy and France, the mortality rate of KTx patients was 30% [25], 28% [47], 18% [33], 17% [27], 26% [30] and 27% [14], respectively. These data are derived from various case reports and studies. These published reports and studies have shown an unusually high mortality rate in comparison to the 1% to 5% in the general population [14][26].

5. Vaccinating Kidney Transplant Recipients

Vaccination has emerged as a crucial tool for COVID-19 management. Several vaccines for influenza, pneumococci, hepatitis B, zoster and human papillomavirus are standard and are also directed for waiting list

patients as well as kidney transplant patients. A majority of the patients respond effectively to these vaccines. According to an international organization's recommendations on COVID-19, immunocompromised patients, including kidney transplant recipients, are prioritized for vaccination [64][65]. However, this guidance has been released without any prior clinical trials as of 24 May 2021. A study in March 2021 by Benotmane et al. indicated a positive response of these patients to the mRNA COVID-19 vaccine [66].

There are very few available reports and studies related to the efficiency and effects of the COVID-19 vaccines on renal transplant and hemodialysis patients. The COVID-19 vaccines that do not have the live virus in their composition can be administered to KTx recipients as the live vaccines can cause vaccine-related disease. The vaccines that do not contain replication-competent SARS-CoV-2 virus have no risks of COVID-19 infection [67][68][69]. The Centers for Disease Control released guidelines for vaccinating immunocompromised patients, given that they do not report any contradictions or allergic reactions to any of the vaccine components [70]. Additionally, it placed stress on informing and counselling the patients about the risks, safety and effectiveness of the vaccines, whose benefits outweigh the potential risks of the COVID-19 vaccine [70][71]. Despite the concern of replication-deficient viral vector-based medicines, Saima et al. reported no concerns for vaccinating immunocompromised persons [72]. Billany et al. and Attias et al. reported a robust antibody response of 80% seropositivity after the first and second dose of vaccines, respectively, in these patients [73][74]. However, the effect of vaccination after the first and second dose was reported to be comparatively low in patients with CKD, KTx or patients on hemodialysis [75][76]. There were no reported cases of organ rejection or severe allergic reaction due to vaccines in transplant recipients. Further, it was also reported that KTx patients were advised to wait for three months after surgery to become vaccinated. This stipulated time is one month for other organs that are transplanted. Patients waiting on a waitlist or undergoing a transplant were also guided to become vaccinated and ideally wait for 14 days after vaccination for the surgery [77]. In the case of acute cellular rejection, immunization should be avoided until the rejection episode has passed. If the patient has gone through anti-CD20 monoclonal antibody treatment, a 6-month interval is recommended between the last rituximab and the SARS-CoV-2 vaccine [78].

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