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Review

SARS-CoV-2 in Kidney Transplant Recipients: A Systematic Review

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global healthcare crisis. Kidney transplant (KTx) patients and the patients with chronic kidney disease are two of the most vulnerable populations to the risks of coronavirus disease 2019 (COVID-19). A systematic literature search on PubMed and Web of Science was conducted. We analyzed published case reports, case series and articles on COVID-19's clinical presentation, management, outcomes and vaccination among kidney transplant recipients. A total of 33 studies were included in the study, which included 1676 KTx recipients and 108 waiting list patients infected with COVID-19. These studies reported the clinical presentation, management and immunosuppressive adjustment among the KTx recipients. The remaining studies focused on other aspects, such as vaccination and transplantation, during the COVID-19 pandemic. Mortality due to COVID-19 was observed to be the highest for KTx recipients, followed by patients on hemodialysis, and lowest in the general population. There is no definitive treatment of COVID-19 yet, and managing transplant patients is enigmatic of this: the treatment is based on symptom management. There is an urgent need for guidelines on managing kidney transplant recipients and immunosuppressive adjustments for the course of COVID-19 treatment.

Keywords: kidney transplant; SARS-CoV-2; COVID-19; treatment; vaccination; transplant

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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 [15–18]. 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].

The aim of this article was to systematically review the available published literature regarding renal transplant recipients and patients on waiting lists diagnosed with COVID-19 all over the world. This paper further deciphers the impact of COVID-19.

2. Materials and Methods

2.1. Search Strategy

A systematic literature search of the articles indexed in the PubMed and Web of Science databases was performed to obtain relevant studies. The search was conducted as of 24 May 2021 without any language restriction. The terms used for search included "COVID-19", "SARS-CoV-2", "kidney transplant" and "chronic kidney disease". Relevant literature reviews and references of included studies were also searched to spot other relevant analyses. This review was conducted in accordance with preferred reporting items for systematic and meta-analysis (PRISMA) guidelines. The full search strategy is depicted in Figure 1.

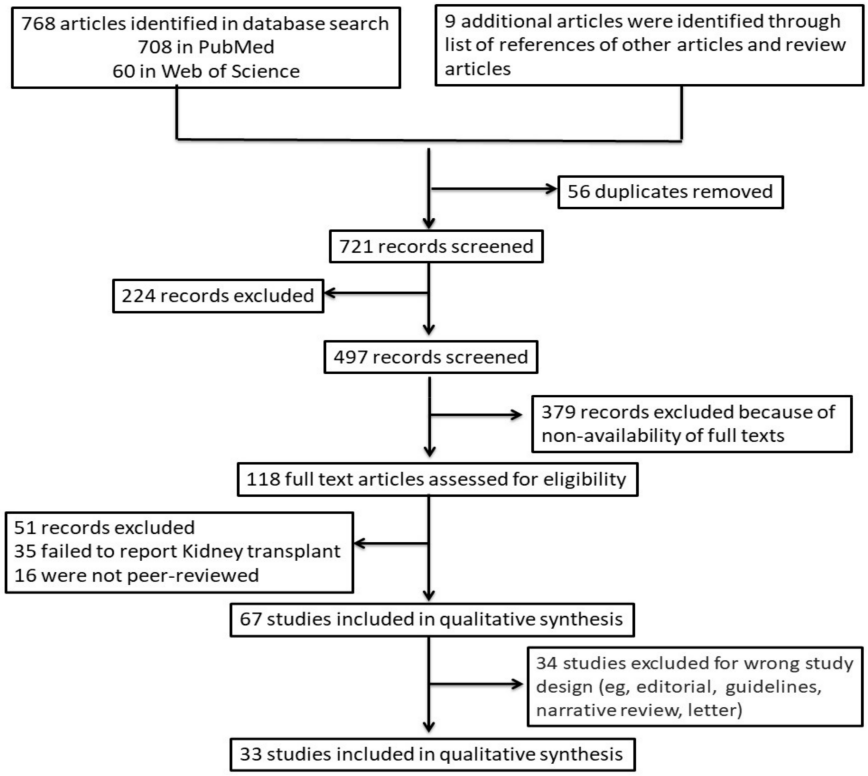

Figure 1. PRISMA flow diagram of included articles.

2.2. Study Selection

We included studies and case reports published until 24 May 2021 that investigated the impact of COVID-19 on KTx recipients. We considered all kinds of published studies—randomized control trials, non-randomized prospective cohorts, retrospective cohorts, case reports and case series. Inclusion and exclusion criteria were developed to facilitate extensive searching and screening for published studies and case reports relevant to COVID-19 and kidney transplantation. All studies were analyzed in accordance with the mentioned criteria: non-KTx patients, non-English publications, inaccessible full texts, and non-peer reviewed studies were all excluded from the review. Studies including KTx patients infected with SARS-CoV-2 were included in this review.

The titles and abstracts of the articles were reviewed by N.K. After the initial screening, the full texts of the articles were reviewed by N.K., R.R. and A.G., which further screened the publications. If the reviewing authors could not reach to a consensus for the inclusion/exclusion of any specific article, then author M.P.S. was contacted and the author's adjudication was sought.

3. Results

A total of 33 studies were included in this review. Out of these 33 studies, 24 studies reported 1676 KTx recipients and 108 waiting list patients who tested positive for COVID-19 via RT-PCR or with an antigen positive SARS-CoV-2 test. Fifteen additional articles were also included in this review which explain the prognosis of COVID-19 infection in the vaccinated KTx patients and the efficacy of the vaccines.

3.1. 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 [14,19,23–36] cough [14,19,23–35], dyspnea [14,19,23–28,30–33,35–37] diarrhea [14,19,23–27,30–32,34,36,37], myalgia [19,23–26,28–30,32,36] 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 [14,30–33,37], 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) [14,23,31–33,36,38–40]. 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 FK	No death
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

Table 1. *Cont.*

Study	Place	Sample Size (N) *	Clinical Presentation #	Treatments #	Immunosuppression Adjustment #	Mortality
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, diarrhea, shortness of breath	HCQ, AZ	Decrease in MPA, MMF and FK	3
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

* Sample size of only KTx recipients is mentioned above and not of the controlled group or other transplant patients. # The mentioned symptoms, treatment or 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; EL, eculizumab; FR, favipiravir; GC, glucocorticoids; HCQ, hydroxychloroquine; Ig, immunoglobulin; LL, leronlimab; LR, lopinavir-ritonavir; OR, oseltamivir; PT, pipperomycin; RD, remdesivir; SL, sarilumab; SX, Selinexor; TL, tocilizumab; VM, vancomycin. IMMUNOSUPPRESSIONS—AMB, antimetabolite; AZT, azathioprine; BC, belatacept; CNI, calcinerium inhibitor; FK, tacrolimus; MMF, mycophenolate mofetil; MPA, mycophenolate acid; PS, predeminisolane.

The number of KTx patients admitted to ICUs varied greatly from 20.2% of the patients in a study by Oto et al. to 52% in a study by Rinaldi et al. [23,27]. Caillard et al. reported bacterial infection in 19.8% of the KTx patients [31]. Mechanical ventilator support was also provided to the patients, though much data are not available on this aspect, except in the study conducted by Chavarot et al. and Caillard et al., who reported that 29% of the KTx recipients infected by COVID-19 disease required mechanical support [30,31].

The cases of patients being affected by mucormycosis were reported around the world and particularly in India [45]. There have been at least 14,872 cases of mucormycosis in India until the third week of May [46]. The symptoms included: one-sided facial swelling,

headache, sinus, black lesions on nasal bridge or in mouth, fever and chest pain. It was reported to have a mortality rate of 54% [47].

The primary reasons that facilitated the condition of mucormycosis in patients with COVID-19 were low oxygen, diabetes, hyperglycemia, acidic medium, high iron levels, immunosuppression and prolonged hospitalization. The 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 rampant use of steroids in the treatment of patients with COVID-19 infection and conditions relating to existing co-morbidities, such as diabetes, were 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 [45,48–57].

3.2. Treatment and Immunosuppressant Adjustments

There is no standard or confirmed 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 COVID-19 patients for both transplant and non-transplant categories as reported in the majority of the studies [14,19,23,27,30–34,37,42,47]. Azithromycin [19,23,30–33,37,39,41,47], tocilizumab [14,27,30–33,36,37,42,47], remdesivir [31,32,36,41,42,44], lopinavir/ritonavir [42,44,58–60], darunavir/cobicistat [24,27,36], favipiravir [23,32,39], oseltamivir [23,31,39], antibiotics [19,23,24,31,32,36,39,41–43] 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 [49–51].

3.3. 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].

3.4. 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 [67–69]. 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].

3.5. Comparing the Impact of COVID-19 among CKD, Kidney Transplant and General Population Patients

The management of KTx recipients diagnosed with COVID-19 is challenging. A study by Mamode et al. from London, being one of the highest prevalent areas for COVID-19, reported a mortality rate of 30% among kidney transplant recipients. This coincides with the mortality rate of waiting list patients, which was 27%. Among the transplant patients, 20.2% of the patients needed ventilator support and 15.6% of patients on the waiting list for a transplant needed ventilator support. The symptoms of COVID-19, including

fever, fatigue nausea, diarrhea and headache, were observed to be higher among the KTx recipients than in waiting list patients [25].

In the Rinaldi et al. study cohort, no significant difference was found in 30-day survival among solid organ transplant patients and non-transplant patients. A higher rate of infections was observed in SOT patients than in the non-transplant patients. Approximately 50% of the transplant patients had reported severe respiratory failure against 33% of non-transplant patients. The ICU admission among transplant patients was found to be 52% against 19.3% among the non-transplant patients [27]. Chavarot et al. compared the survival rate of kidney transplant patients to the non-transplant patients, and found that the survival of transplant patients was similar to that of non-transplant patients who had similar comorbidities, thereby indicating that immunosuppressant does not pose any implications or risk of severe COVID-19 infection [30].

Meester et al. reported that by the end of first COVID-19 wave, i.e., 2 March 2020 to 25 May 2020, 5.31% of the hemodialysis patients, 1.4% of the KTx recipients and 0.64% of the general population of Flanders, Belgium were affected by COVID-19. The mortality rates of COVID-19 were found to be 14%, 29.6% and 15.3% among KTx recipients, hemodialysis patients and the general population, respectively [63] Similarly, in a New York, USA-based study by Schapiro et al., 34% of the waiting list patients died of COVID-19 infection against the 16% of deaths in transplant patients. Moreover, 50% of the patients with a transplant had acute kidney injury and 9% of the transplant patients lost graft [40].

Caillard et al. compared KTx recipients with non-transplant patients infected with COVID-19. The symptoms among the groups were similar, including fever, cough, dyspnea and diarrhea. However, the acute kidney injury rate found in transplant recipients was very high at 45.8%, in comparison to non-transplant patients, where 13.8% of the patients had AKI. Renal replacement therapy was required in 13.2% of the KTx recipients after COVID-19, in comparison to 9.9% in the non-transplant patients [31].

3.6. Transplantation during COVID-19 Pandemic

The COVID-19 pandemic has significantly affected transplant surgery and many other elective surgeries. Early reports from Wuhan, China, reported an increased morbidity and mortality in patients undergoing surgery with asymptomatic COVID-19 infection [79]. Therefore, transplant evaluations and surgeries were paused as an early response to the pandemic [8]. It has been recognized for a long time that kidney transplantation offers a better prognosis over dialysis [80–82]. However, the risk of COVID-19 infection is unknown and limited data are available. A mixed result is observed from the published studies, where a risk of the severity and morbidity of COVID-19 has been found among KTx recipients and patients on waiting lists or dialysis [26,27,30,31,40,63]. Ravanan et al. studied the UK registry and found that the waiting list patients are more likely to become infected and less likely to die of COVID-19 than KTx recipients [83].

The American Society of Transplant Surgeons (AST) and The Transplantation Society developed recommendations for donor and recipient safety [84–86]. It stated that COVID-19-recovered individuals can be evaluated for organ donation and donate after 28 days of symptom resolution and after a provision of a negative COVID-19 report. Kanchi et al. reported two cases of kidney transplant surgeries where, in the first case, the recipient tested positive, and in the other, both donor and recipient tested positive for COVID-19 [87]. After 2–4 weeks of testing negative, the transplant surgery was performed, and both the recipients were reported to be doing well in the follow ups.

Further the decision to perform the transplant depends on several factors and situations. It depends upon the spread of COVID-19 in the area where the recipients and donors are living, the availability of transplant surgeons, transplant teams and the medical equipment [88].

Various international organizations have formed guidelines for kidney transplant during the times of COVID-19. It is recommended for the transplant team and doctors to encourage the recipient to become vaccinated for SARS-CoV-2 at least 14 days prior

to transplant surgery. It is recommended that other household members of the recipients should also become vaccinated themselves [69]. After transplantation, the best time for becoming vaccinated is three months post-transplant, given that the recipient does not encounter any case of infection or acute cellular rejection [78]. Even after vaccination, COVID-19-appropriate behaviors should be followed by the recipient as well as the household members.

3.7. Occurrence of COVID-19 among Vaccinated Kidney Transplant Patients

After the first dose of the SARS-CoV-2 vaccine, only 11–17% of the patients developed anti-spike antibodies after 20–28 days of vaccination [66,76,89]. Among the double-vaccinated KTx recipients, 36–59% had developed antibodies after 28 days of vaccination [90–93]. A study by Caillard et al. on the occurrence of coronavirus disease 2019 in 55 solid organ transplant patients after two doses of mRNA-based COVID-19 vaccine reported that almost 27% of the patients required oxygen support. Forty-six patients had received the BNT162b2 (Pfizer-BioNTech) and nine have received the mRNA-1273 (Moderna) vaccines. Further, approximately 11% of the patients were admitted to ICU, and 5.5% of the patients died. Out of these 55 patients, three patients were kidney–pancreas transplant recipients, and the rest were kidney recipients [94].

A study from India reported on four KTx recipients infected with COVID-19. Two of the patients received a single dose and the other two received a double dose of Oxford-AstraZeneca (Covishield). The study speculated that the response of the KTx patients to the vaccine was suboptimal, and the recipients were more prone to severe COVID-19, even after vaccination. In this study one of the patients died after 8 days of admission, two patients needed ventilator support and one patient recovered (shown in Table 2) [95]. Aslam et al. reported on four cases of patients with COVID-19 among solid organ transplant patients, out of which one was a KTx recipient. The patient received the BNT162b2 vaccine and was diagnosed with COVID-19 after 72 days of the second dose. The symptoms of the patient were moderate, with diarrhea, and they had no respiratory symptoms [96]. Another study by Ali et al. on the development of COVID-19 infection among solid organ transplant patients presented 14 cases of transplant patients with 10 KTx recipients. Six out of ten patients had received BNT162b2, three received mRNA-1273 and one received the Ad26.COV2.S (Janssen/Johnson & Johnson) vaccine for COVID-19. All the patients were alive, except for two, who were still hospitalized. Four patients presented severe symptoms, while the rest experienced mild and mild–moderate symptoms [97].

Table 2. Clinical presentation, treatments and outcomes of vaccinated COVID-19 in KTx recipients.

Patient	Age (Years)	Time from Tx	Vaccine	No. of Doses	Time from Vaccine (Days)	Clinical Presentation	Severity of COVID-19	Treatments	Outcomes	Reference
I.	71	192	Oxford-AstraZeneca	2	20	Fever, cough, shortness of breath	-	TF, DX, RD, MV	Died	[95]
II.	51	18	Oxford-AstraZeneca	2	13	Fever, cough, diarrhea	-	AZ, DX, CP, MV	Ventilator	[95]
III.	46	108	Oxford-AstraZeneca	2	23	Fever, cough, shortness of breath, weakness	-	AZ, DX, RD	Ventilator, dialysis dependent	[95]
IV.	67	72	Oxford-AstraZeneca	2	8	cough	-	AZ	Recovered	[95]
V.	67	72	BNT162b2	2	72	Diarrhea	Moderate	RD	Recovered	[96]
VI.	44	16	BNT162b2	2	11	Fever, cough, shortness of breath	Severe	RD, DX	Recovered	[97]
VII.	68	16	mRNA-1273	2	4	Cough, weakness	Mild	None	Recovered	[97]
VIII.	58	19	Ad26.COV2.S	2	19	Diarrhea	Mild	MAB, RD	Inpatient	[97]
IX.	72	2.5	BNT162b2	2	20	Fever, cough, diarrhea	Mild–moderate	MAB	Recovered	[97]

Table 2. *Cont.*

Patient	Age (Years)	Time from Tx	Vaccine	No. of Doses	Time from Vaccine (Days)	Clinical Presentation	Severity of COVID-19	Treatments	Outcomes	Reference
X.	27	11	BNT162b2	2	43	Cough	Mild	MAB	Recovered	[97]
XI.	69	18	BNT162b2	2	25	Fever, shortness of breath	Severe	RD, DX	Inpatient	[97]
XII.	71	24	mRNA-1273	2	18	Fever, diarrhea, vomiting	Severe	RD, DX, MAB, CP	Recovered	[97]
XIII.	59	47	mRNA-1273	2	36	Headache, body ache, weakness	Mild	None	Recovered	[97]
XIV.	54	48	BNT162b2	2	45	Weakness	Mild	None	Recovered	[97]
XV.	52	53	BNT162b2	2	40	Cough, body aches	Mild–moderate	MAB	Recovered	[97]
XVI.	55	83	BNT162b2	1	7	-	-	None	Recovered	[98]
XVII.	58	38	BNT162b2	1	14	-	-	None	Recovered	[98]
XVIII.	55	58	BNT162b2	1	14	-	Critical	RD, DX	Died	[98]
XIX.	60	48	BNT162b2	1	18	-	-	None	Recovered	[98]
XX.	51	5	BNT162b2	1	21	-	Critical	RD, DX, CP	Died	[98]
XXI.	57	49	BNT162b2	1	22	-	-	None	Recovered	[98]
XXII.	42	64	BNT162b2	1	24	-	Critical	DX, CP	Died	[98]
XXIII.	51	23	BNT162b2	2	4	-	Mild	BAM	Recovered	[98]
XXIV.	35	27	BNT162b2	2	9	-	Severe	None	Recovered	[98]
XXV.	34	13	BNT162b2	2	12	-	Mild	None	Recovered	[98]
XXVI.	34	16	BNT162b2	2	12	-	Mild	None	Recovered with elevated creatinine	[98]
XXVII.	62	246	BNT162b2	2	25	-	Critical	RD, DX, CP	Died	[98]
XXVIII.	64	25	BNT162b2	2	33	-	Severe	RD, DX, CP	Recovered	[98]
XXIX.	49	7	BNT162b2	2	35	-	Severe	DX, CP	Recovered	[98]
XXX.	65	41	BNT162b2	2	36	-	Critical	RD, DX	Died	[98]
XXXI.	26	154	BNT162b2	2	38	-	-	None	Recovered	[98]
XXXII.	40	237	BNT162b2	2	43	-	-	None	Recovered	[98]
XXXIII.	77	9	BNT162b2	2	46	-	Severe	DX	Recovered	[98]
XXXIV.	78	59	BNT162b2	2	52	-	Mild	DX	Recovered	[98]
XXXV.	72	94	BNT162b2	2	53	-	Critical	RD, DX, CP	Died	[98]
XXXVI.	68	23	BNT162b2	2	53	-	-	None	Recovered	[98]
XXXVII.	57	121	BNT162b2	2	54	-	-	None	Recovered	[98]
XXXVIII.	63	69	BNT162b2	2	73	-	Severe	-	In hospital	[98]
XXXIX.	26	250	BNT162b2	2	85	-	-	None	Recovered	[98]
XL.	70	45	BNT162b2	2	-	-	Critical	RD, CP	Died	[98]

Treatments—AZ, azithromycin; BAM, bamlanivimab; CP, convalescent plasma; DX, dexamethasone; FR, favipiravir; MAB, monoclonal antibody; MV, mechanical ventilation; RD, remdesivir; TF, tofacitinib.

On the basis of a small study on 12 solid organ transplant recipients, it was found that the Ad26.COV2.S vaccine showed a poor humoral response in immunocompromised patients, with only two patients reporting the development of antibodies against the spike protein in COVID-19 patients. The study also suggested that the Janssen vaccine may even lower the humoral immunity in immunocompromised patients in contrast to the mRNA-based vaccines [99]. A strong response to the mRNA-based vaccine was observed among KTx recipients who had a history of coronavirus disease 2019 infection [100–102]. The antibody titers in these patients were similar to the non-immunocompromised patients.

4. Implications for the Future

The current data in this review are insufficient to formulate generalized statements. There are two major key points for the future in the current pandemic situation and considering the upcoming third wave of COVID-19. The first point is that a large-scale multicenter evaluation of the symptoms, treatments and effects of COVID-19 in KTx recipients is needed, especially in developing countries such as India, which are severely affected by SARS-CoV-2. A protocol or standard treatment and intervention should be planned and implemented for the best possible care of the COVID-19-positive KTx recipients.

The second point is that we need to be prepared in advance for the next wave of the pandemic. This includes vaccinating the most vulnerable patients and readying ourselves for all the complications that come along with COVID-19 in already high-risk patients.

5. Conclusions

From our review of the existing literature to date, we can draw several preliminary conclusions about the effects of COVID-19 in KTx recipients. First, the symptoms of COVID-19 in KTx recipients and patients with CKD/on waiting lists are similar to the general population. The chances of becoming infected from the virus are greater among the waiting list patients who are on hemodialysis treatment than among the KTx recipients, and it is the least among the general population. The severity of the COVID-19 infection is highest among KTx recipients, followed by patients on hemodialysis and on the waiting list, and least in the general population. Mortality due to COVID-19 is observed to be the highest in KTx recipients, followed by patients on hemodialysis, and it is lowest in the general population. Second, the treatment of the COVID-19-infected KTx recipients is similar to the non-transplant patients; i.e., the treatment is based on symptom management. Immunosuppressants are adjusted on a patient-to-patient basis, depending upon the symptoms, severity and recovery trajectory. In addition, the prevalence, incidence and effect of mucormycosis needs to be studied carefully, as solid organ transplant recipients are one of the most vulnerable to mucormycosis. Third, vaccinations are advisable for KTx recipients, as well as for the dialysis patients. They should become vaccinated with vaccines that do not contain the replication-competent SARS-CoV-2 virus and any component that they are allergic to. Fourth, elective surgery/transplantation should be performed while assessing the risk of COVID-19 and only when any other infection risk is minimum. There should be no extra burden to the staff or hospital during pandemic and, if avoidable, the transplantation should be postponed, which will help prevent the donor as well as recipient from catching COVID-19 infection. The ideal time for becoming vaccinated is at least 2 weeks prior to transplant surgery, and three months post-transplant if no incident of acute rejection is observed post-transplant.

6. Limitations

The current review was performed in order to gain knowledge about the impact of COVID-19 on kidney transplant patients. It is important to acknowledge the limitations of this review. COVID-19 research is rapidly evolving and some of the aspects have very few or no published data. Most of the literature includes case reports and case series, all of which have a great potential of bias. Therefore, it is difficult to draw substantial conclusions. Further studies and cohorts are required to determine the role of COVID-19 in CKD and KTx recipients. The article extracted the articles for review from two sources which may lead to the loss of other relevant articles from other sources. The second limitation of the study is that the article does not specify the different variants of SARS-CoV-2 virus and talk about the varying impact of disease on transplant patients. Thirdly, the published data on the impact of COVID-19 on vaccinated KTx patients are very limited, because of which we could not draw any conclusion on the efficiency of the vaccines in kidney transplant recipients in terms of disease prognosis, severity and duration of the infection.

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