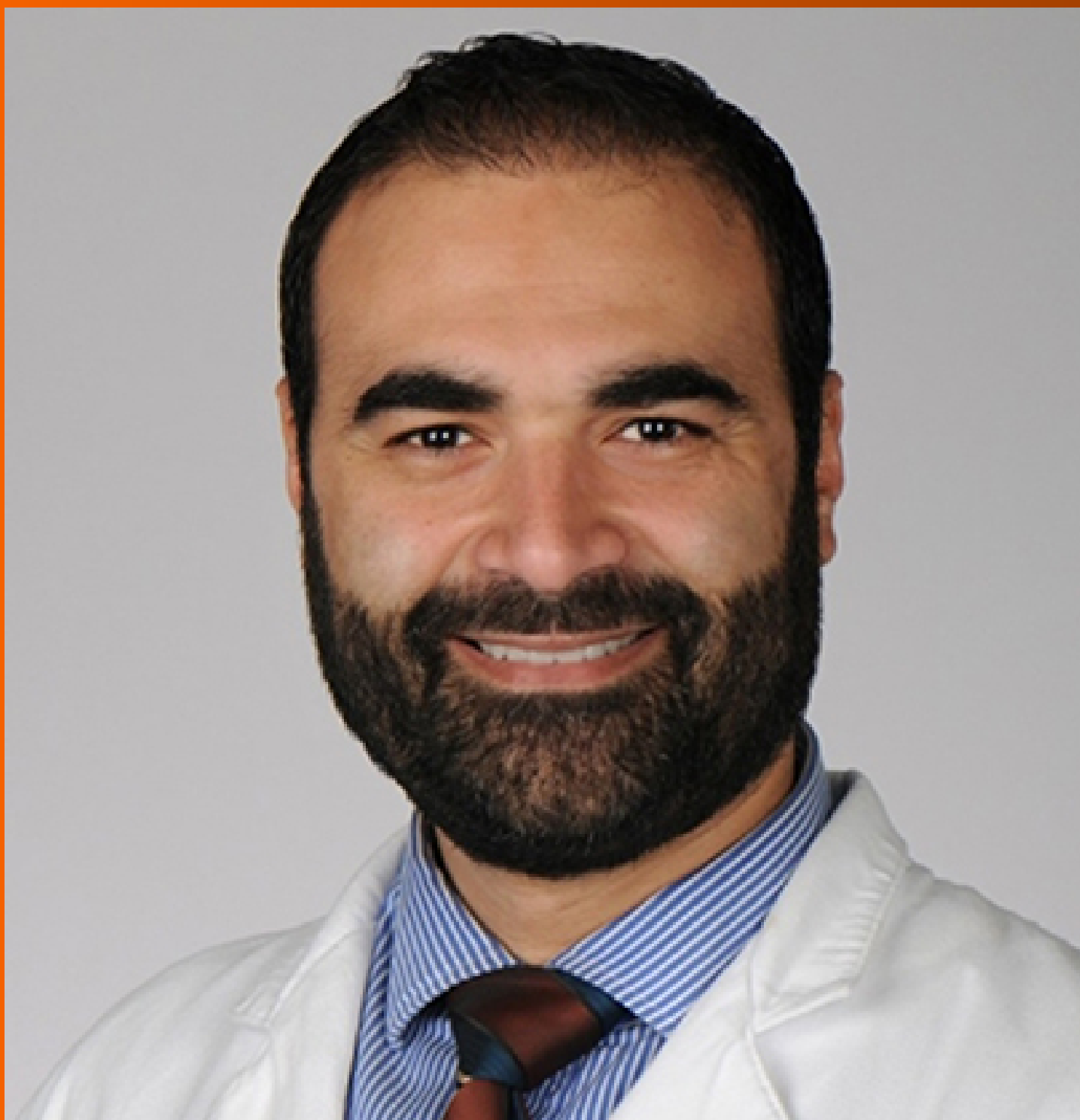


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Solid organ transplantations and COVID-19 disease

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Abstract

Tens of thousands of people worldwide became infected with severe acute respiratory syndrome coronavirus-2. Death rate in the general population is about 1%-6%, but this rate rises up to 15% in those with comorbidities. Recent publications showed that the clinical progression of this disease in organ recipients is more destructive, with a fatality rate of up to 14%-25%. We aimed to review the effect of the pandemic on various transplantation patients. Coronavirus disease 2019 (COVID-19) has not only interrupted the lives of waiting list patients; it has also impacted transplantation strategies, transplant surgeries and broken donation chains. COVID-19 was directly and indirectly accountable for a 73% surplus in mortality of this population as compared to wait listed patients in earlier years. The impact of chronic immunosuppression on outcomes of COVID-19 remains unclear but understanding the immunological mechanisms related to the virus is critically important for the lifetime of transplantation and immune suppressed patients. It is hard to endorse changing anti-rejection therapy, as the existing data evaluation is not adequate to advise substituting tacrolimus with cyclosporine during severe COVID-19 disease.

Key Words: COVID-19; SARS-CoV-2; Solid organ transplantation; Mortality; Immunosuppression; Comorbidity

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Core Tip: Coronavirus disease 2019 (COVID-19) has not only interrupted the lives of waiting list patients; it has additionally impacted transplantation policies, transplant surgeries and broken donation chains. Revised guidelines should advise to continue cyclosporine use as an immunosuppressant to the patients during COVID-19 disease excluding some of patients having kidney failure, severe leucopenia or high serum cyclosporine levels.

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INTRODUCTION

Introduction and aim

Tens of thousands of people worldwide became infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1]. When the disease is clinically symptomatic; it presents with fever, cough, lymphopenia, dyspnea and, multiorgan failure in severe cases[2]. Death rate in the general population is about 1%-6%, but this rate rises up to 15% in those with comorbidities[3]. Current publications showed that the clinical progression of this disease in organ recipients is more destructive, with a fatality rate of up to 14%-25%. We aimed to review the effect of the pandemic on various transplantation patients[4].

Negative effects of coronavirus disease 2019 in increasing waiting list of organ transplantations

Coronavirus disease 2019 (COVID-19) has not only interrupted waiting list patients' lives; it has also affected transplantation strategies, transplant surgeries and broken donation chains. COVID-19 was directly and indirectly accountable for a 73% surplus in mortality of this population as compared to wait listed patients in former years[5].

High COVID-19 afflicted areas observed more than a 2.2 times greater waiting list fatality as compared to prepandemic mortality in the United States[6]. In the United Kingdom, 10% of wait listed patients who developed COVID-19 died[7]. In France, as many as 42% of wait listed deaths in March and April 2020 were caused by COVID-19 [5].

Kidney transplant waiting list deaths increased by 43%, the largest in any solid organ transplantation (SOT) patient group on the waiting list[8,9]. In perspective, there was a 12% increase in deaths in patients on the lung transplant waiting list, an 8% increase in deaths on a liver transplant waiting list, and a 36% increase in deaths in patients on a heart transplant waiting list[10].

Transplant and waiting list patients have similar death rates after admission to the hospital for COVID-19 disease. A study has demonstrated a low absolute fatality risk from COVID-19 in transplanted and waitlisted cases, but a high and similar death rate when admitted to the hospital, of around 30%. Death rate was higher in elderly transplant recipient cases[11].

UNDESIRABLE EFFECTS OF IMMUNOSUPPRESSION ON COVID-19 IN TRANSPLANTATION PATIENTS

The impact of chronic immunosuppression on outcomes of COVID-19 remains unclear but understanding the immunological mechanisms related to the virus is critically important for the lifetime of transplantation and immune suppressed patients.

Given the reduced T-cell immunity, transplant recipients are estimated to be at a greater risk for serious bacterial and viral infections. The difficult problem is when a coronavirus-infected immunosuppressed and SOT patient is taking either intravenous immunoglobulin (IVIG), steroids, calcineurin inhibitors or mycophenolic acid. SOT itself covers various clinical conditions/issues resulting from kidney, liver, heart and lung transplantations (Table 1).

Angiotensin-converting enzyme-2 and dipeptidyl peptidase, expressed in proximal tubular cells, are identified as receptors for SARS-CoV and MERS-CoV[12]. The possible explanation for acute renal injury is the uptake of SARS-CoV-2 virus into the proximal tubular epithelium and virus infection inducing CD68+ -macrophage infiltration and enhancing complement C5b-C9 deposition on tubules[13].

Acute renal injury is one of the most common complications of COVID-19. It was seen in 30%-89% of patients with kidney transplantation. Acute renal injury has developed as a result of many factors like decreased renal perfusion and cytokine storm[14]. To date, minimizing the utilization of antivirals and immunosuppressive

Table 1 Therapeutic agents used during solid organ transplantation period and their side effects

Agents	Mechanism	Side effects
IVIG	Reduces HLA sensitivity. The goal of the IVIG therapy is to lower the level of HLA antibodies and limit their ability to attack a transplanted organ	Headache, fever, urticaria, eczema, hypotension, anaphylactic shock, TRALI, immune thrombocytopenic purpura. Delayed side effects: Renal impairment, transfusion related infection
Glucocorticosteroids	Mimic the effects of cortisol side effects block T-cell derived and antigen presenting cell derived cytokine expression	Hypertension, hirsutism, susceptibility to infection, osteoporosis, necrosis, insulin resistance, growth retardation
Calcineurin inhibitors (cyclosporine, tacrolimus)	Inhibition the key signaling phosphatase calcineurin, which is an enzyme that activates T-cells of the immune system	Nephrotoxicity, promoting of the <i>de novo</i> cancers, metabolic disorders such as diabetes, dyslipidemia, gingival hyperplasia, hirsutism, hypertension, susceptibility to infection
Antiproliferative agents (Mycophenolic acid, azathioprine)	Inhibiting purine base synthesis and arresting T- and B-cell proliferation	Nausea, sleep disturbance, headache, constipation, diarrhea, weakness, fever, hematuria
mTOR inhibitors (sirolimus, everolimus)	Alternative for calcineurin inhibitors and antiproliferatives. T-cell proliferation inhibition. Binds to the specific cytosolic protein FKBP-12	Hypertension, hyperlipidemia, anemia or thrombocytopenia, headache, proteinuria, interstitial lung disease, mouth ulcers
Azathioprine	Decrease DNA and RNA synthesis reduce the production of lymphocytes	Nausea, hepatotoxicity, leukopenia, thrombocytopenia, malignancies

FKBP: FK506 (tacrolimus) binding protein; IVIG: Intravenous immunoglobulin; TRALI: Transfusion related acute lung injury; mTOR: Mechanistic target of rapamycin.

therapy has been recommended, but the evidence has been weak to support these recommendations[1]. Hypothetically, conversion to cyclosporine, in kidney transplant patients with COVID-19 has both antiviral potency and immunomodulatory effects; it may also help to avoid graft rejection during the infection[1].

Several studies have reported that immunosuppression may be a possible risk factor for coronavirus-related pneumonia in a patient[13]. For kidney transplant recipients diagnosed with SARS-CoV-2, it may be reasonable to use cyclosporine because of its antiviral and immune modulatory effects[13]. According to various clinical studies, severe pneumonia has been more widely reported in patients receiving anti-rejection and induction therapies, possibly due to immunosuppression[15].

The management of heart transplant recipients becomes more complex as these heart transplant patients require more intense immunosuppression than other SOT recipients[16]. In addition to the present complexity, COVID-19 has a potential effect on both primary and secondary myocardial injuries[17]. These cases are constantly utilizing long-term immunosuppressive therapy and at a high risk to develop unwanted effects. Although they have adequate heart function, this population must be thought of as very brittle owing to the existence of several comorbidities like chronic renal disease associated with a long exposure to immunosuppressants. In a transplanted cases' cohort, time-dependent comorbidities along with older age, such as calcineurin inhibitor nephrotoxicity and other common complications of immunosuppressive management, could also be harmful[18].

Transplant recipients are thought by some authors as a high-risk group for COVID-19 since they take lifetime immunosuppressive treatment. Immunomodulatory agents could improve immune reaction, but this could yield to an escalation in viral load and postponed disease salvage. Remarkably, calcineurin inhibitors, the most commonly used immunosuppressive agent in lung transplant recipients, have shown impressive capacities to inhibit the replication of coronaviruses. Therefore, it was suggested that basic immunomodulation could defend lung transplant patients against the most severe clinical pictures of COVID-19 disease[19].

Calcineurin inhibitors, antimetabolites, and glucocorticosteroids are the most commonly used as standard immunosuppressants; nonetheless, in COVID-19 confirmed patients, antimetabolites were generally stopped while prescription of glucocorticosteroids was continued in management or even amplified in dosage. It was thought as essential to use suitable doses of glucocorticosteroids through the process, as it could subdue hyperinflammatory reaction and stimulate the recovery from pneumonia without severe unwanted effects[20].

Impact of co-infections (fungal) with COVID-19 in transplantation patients

Impact of co-infections (bacterial or viral) with COVID-19 disease in SOT patients

could be severe and lethal. To the best of our knowledge, specific co-infections (bacterial or viral) related with SARS-CoV-2 in SOT patients have not been widely reported. However, SARS-CoV-2 might raise the risk of invasive pulmonary aspergillosis (IPA) development in these patients. Although several case reports and small series have been described in the literature, infrequent information is obtainable concerning COVID-19-related IPA in SOT cases. A case of a renal SOT recipient with severe COVID-19 was later diagnosed with IPA. After beginning of isavuconazole with nebulized liposomal amphotericin B combination treatment and the withdrawal of immunosuppression, IPA was improved[21].

Other risk factors for COVID-19 development and mortality in transplantation patients

SOT cases with COVID-19 had a tendency to greater mortality compared with non-SOT controls, although it was not always found to be statistically significant[20,22]. Immunosuppression and comorbidities might put SOT patients at a higher risk from COVID-19, as proposed by new case series[23]. In the overall literature, some factors were shown to be independently related with COVID-19 which included non-white race and comorbidities, comprising obesity, diabetes, asthma and chronic obstructive pulmonary disease[24]. Nevertheless, no factors were demonstrated to be related with fatality, other than being elderly in those who had been transplanted[11].

A few studies have clearly compared consequences between SOT and non-SOT patients with COVID-19 disease. A retrospective matched cohort single-center study evaluated effects of COVID-19 and the effect of immunomodulation on cytokine release syndrome of COVID-19 in SOT patients. Overall, SOT recipient cases had equal fatality to non-SOT cases, although more SOT cases received tocilizumab (63% *vs* 48%) and steroids (37% *vs* 20%)[25]. In another study, 45 SOT *vs* 2427 non-SOT cases hospitalized with COVID-19 to a health-care system were compared. There were no statistically meaningful differences between SOT and non-SOT in maximum illness severity score, length-of-stay, or mortality. Regardless of a greater risk profile, SOT recipients had a significantly faster drop in disease severity over time compared with non-SOT cases[23]. Chaudhry *et al*[26] compared consequences of 35 SOT cases with 100 non-SOT cases that were admitted with COVID-19 at a single center, and detected that a combined consequence [intensive care units (ICU) admission, intubation, hospital fatality] was similar between these 2 groups, even though comorbidities and acute renal damage were more usual in the SOT case group[26]. Generally, SOT cases were more likely to take COVID-19 specific treatments and to need ICU admission. However, fatality (23.08% in SOT *vs* 23.14% in non-SOT) and highest level of supplementary oxygen needed during admission did not significantly vary between these groups[27].

As a result of the comprehensive literature, mortality in SOT recipients compared to controls (non-SOT recipients) has been detected as similar and the SOT programs should not be stopped and are best to be continued during the SARS-CoV-2 pandemic.

VARIOUS THERAPEUTIC OPTIONS OF COVID-19 DISEASE IN TRANSPLANTED PATIENTS

Convalescent immune plasma (CIP) infusion has been utilized in the therapy of other infectious diseases for more than a century[28], under the notion that passive immunization can push the immune system to prevent the disease progression until a specific immune response is developed in the afflicted person[29]. However, the use of CIP did not improve survival in non-transplant patients with severe COVID-19 disease [29]. According to a randomized control trials study at day 30, no significant difference was reported between the CIP and the placebo groups[29].

A course of IVIG at a dose of 1 g/kg was given as an immunomodulatory therapy in patients with serum immunoglobulin G (IgG) level < 700 mg/dL. Antiviral treatment was not administered in any group. According to a large, randomized open-label trial, dexamethasone was related with lower fatality in patients necessitating mechanical ventilation or supplemental oxygen, compared with standard care[30].

Mycophenolate has a cytostatic effect on activated lymphocytes. In COVID-19, the virus SARS-CoV-2 has a direct cytotoxic effect on CD8⁺ -lymphocytes, thus explaining the relation between lymphopenia and poorer outcomes. Consequently, mycophenolate and SARS-CoV-2 may reveal a synergic side effect on diminishing peripheral lymphocytes, which would be accountable for a deviant immune modification as

shown with other viruses. On the contrary, mechanistic target of rapamycin (mTOR) inhibitors enhance the quality and functionality of memory T-cells and lessen the replication of numerous viruses[31].

Cyclosporine can be beneficial at any moment through the progress of the disease given its impact on the inhibition of viral replication, maintenance of renal graft and down regulation of the immune reaction. Cyclosporine and tacrolimus are the most utilized calcineurin inhibitors in regular clinical practice for inhibition of alloimmune response in transplantation. Calcineurin inhibitors subdue the immune system and the primary action is inhibition of interleukin-2 (IL-2) production in T-cells. Cyclosporine and tacrolimus are chemically different molecules. Calcineurin inhibitors attach to intracellular cyclophilin, which is an immunophilin, and this calcineurin inhibitor-immunophilin complex inhibits nuclear factor of activated T-cells (NFAT). As a result of NFAT inhibition, cytokine transcription and T-cell activation are blocked[32]. The cyclosporine level needed to prevent virus replication surpasses by far the serum levels that characteristically are well below 200 ng/mL[32]. This indicates that the dose utilized to manage most patients with cyclosporine is too low to successfully eliminate the virus. One of the issues is to reach adequate tissue level, as the key virus load is in the respiratory tract and lungs rather than in serum and the cyclosporine concentration in the lungs is lesser than in serum[32]. Additionally, the necessary dosage for vigorously treating severe COVID-19 patients would be 3-6 times greater, which in turn would trigger severe adverse and possible toxic effects, specifically nephrotoxicity[32]. Inhaled cyclosporine has been tried in animals, healthy volunteers and pulmonary transplantation recipients and the pulmonary amount of inhaled cyclosporine is three times more than when systemically administered[32].

Calcineurin inhibitors, such as cyclosporine A and tacrolimus, have a significant role in continuing immunosuppression after SOT. Those medications have a slight therapeutic window, and individual doses and drug management are required. A significant number of cases suffer from short- or long-term calcineurin inhibitors toxicity, with renal dysfunction, hypertension, neurotoxicity and metabolic instabilities [33]. Dose minimization is related to a modest improvement in kidney function, but persistent injury is detected on biopsies if the calcineurin inhibitors are sustained. Calcineurin inhibitor cessation may be the best option by providing calcineurin inhibitors through the early period of immunologic graft damage and then changing them to less nephrotoxic drugs before imperative renal damage happens[34].

Prophylactic lessening of immunosuppression due to fear of COVID-19 disease is not recommended in SOT recipients. With maintenance immunosuppressive management, glucocorticosteroids can be sustained during COVID-19 disease[35]. Sustaining other immunosuppressive medications with lowest effective dose/blood concentration is recommended for cases having mild to moderate COVID-19. Withdrawal of antimetabolites, *e.g.*, mycophenolate mofetil, and maybe inhibitors of mTOR such as sirolimus is recommended in moderate to severe COVID-19. Calcineurin inhibitors may be sustained or replaced for mTOR inhibitors with lower therapeutic levels in moderate to severe COVID-19. If sustained in COVID-19 cases, therapeutic drug watching of calcineurin/mTOR inhibitors and proper dose lessening is suggested in combination with protease inhibitors, hydroxychloroquine/chloroquine, or IL-1/IL-6 receptor antagonists. Checking the hemogram is suggested in cases using antimetabolite drugs or mTOR inhibitors. Drug dose adjustment/evasion should be contemplated for chloroquine, atazanavir, oseltamivir, ribavirin, anakinra, and Janus associated kinase (Jak) inhibitors in cases with organ dysfunctions[36].

Anti-COVID-19 medications, *e.g.*, lopinavir/ritonavir and hydroxychloroquine, have not been tested by laborious clinical trials. These medications may be utilized cautiously for common patients with COVID-19, but for SOT recipients using long-term immunosuppressive management, antiviral medications should be meticulously chosen. Moreover, the senior SOT patients are frequently afflicted with hepatic and renal dysfunction of varying degrees, resulting in worse drug metabolism. The combination of lopinavir/ritonavir and hydroxychloroquine is implicated in extreme tacrolimus trough whole blood levels with unwanted effects[37].

COVID-19 VACCINATION IN TRANSPLANTATION PATIENTS

In transplant recipient patients, the COVID-19 vaccine is a way to protect these patients when there is no definitive cure for COVID-19. On the waiting list of cases with COVID-19, serologic studies have showed that IgM levels increase 5-10 d after infection onset. IgG development classically follows an IgM response development

within 12–14 d of symptom onset in most patients[9]. Follow-up studies suggest that these responses last for at least 5 mo succeeding infection and can confer immunity against repeated SARS-CoV-2 infections[9].

Growing evidence indicates that SOT recipients who take mRNA-based vaccines have low immunization rates[38]. Less than half of the vaccinated transplant cases demonstrated antibodies against the SARS-CoV-2 spike protein[38]. Although immunosuppressant agents are thought to have a key role during this course, the appearance of severe COVID-19 disease after mRNA-based vaccination in immunocompetent or immunocompromised individuals has not yet been described[38]. A possible reason for this might owe to lack of humoral response, together with a restricted or deficient T-cell response, even after the second dose of the vaccination [38]. Live (replication-competent) vaccines are usually contraindicated in immunocompromised subjects due to a risk of vaccine-acquired disease[39]. These vaccines contain intact virions that are engineered to incorporate the gene encoding the SARS-CoV-2 spike protein, and somehow influences the viral vector's capacity to competently infect cells and increases spike gene delivery[39]. It should be emphasized that immunosuppression isn't considered as a contraindication to their use, despite the theoretical concerns with replication-deficient viral vector-based vaccines. SARS-CoV-2 vaccines have significant potential to decrease COVID-19-associated morbidity and mortality among recipients of SOT, including kidney transplants[39].

In a study, 14 SOT recipients were diagnosed with COVID-19 24 d after injection of vaccines. One patient died, 2 patients were hospitalized and 11 patients were recovering at home. 50% of infected cases were hospitalized for the management. There was enough data to issue warnings that immunologically incompetent people should continue to practice firm COVID-19 precautions after vaccination and directions given to the overall population may not be relevant to the SOT patients[40].

SOME ISSUES OF TRANSPLANTATION PATIENTS DURING COVID-19 PANDEMIC

As access to hospitals becomes easier; the determination of SARS-CoV-2 infected patients with mild symptoms which would otherwise be missed in the overall population is increasing.

Fatality rates were lesser than those detected in the age- and gender-matched common population, thereby signifying that chronic immunosuppression could result in a certain protective effect against the most severe types of COVID-19. According to a multi-center study in Istanbul, the usage of cyclosporine was related with a lesser incidence of fatality. On the contrary, rejection treatment was recognized as a risk factor for mortality[15]. Nevertheless, in cases taking mycophenolate, dose lessening, or temporary change to calcineurin inhibitors or everolimus may be considered until complete rescue from COVID-19[31].

It is hard to endorse changing anti-rejection therapy, as the existing data appraised is not adequate to endorse substituting tacrolimus with cyclosporine during severe COVID-19 disease[32]. Nonetheless, revised guidelines should advise to continue cyclosporine use to the cases during COVID-19 except in some of the patients having kidney failure, severe leucopenia or increased serum cyclosporine levels. A change from tacrolimus to cyclosporine would be found only on affirmative observational documents with a supposed advantage for COVID-19 illness, but with a likely greater risk of refusal and controlled studies are necessary to examine whether this change is suitable or not[32]. We need to identify which SOT recipients benefit from specific therapies, the ideal timing of these therapies and the balance of benefits and risks of these therapies, such as late secondary infections. We have to encourage clinical trials and observational researches in the future to incorporate SOT recipients. Long-term follow up of SOT recipients will be important in order to clarify these guidelines. For the safety of recipients, testing donors for SARS-CoV-2 has become a cornerstone of kidney transplant practice[9].

CONCLUSION

Although both negative effects of COVID-19 on increasing waiting list and undesirable effects of immunosuppression on COVID-19 disease in SOT patients; the current literature data support continuation of transplant programs during the COVID-19 era

[11].

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