COVID-19 PANDEMIC AND KIDNEY TRANSPLANTATION

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Infections are a common complication arising after kidney transplantation with a high rate of morbidity and mortality. Since the beginning of the COVID-19 pandemic, it has been reported that the kidney transplant recipient population have the worst outcome and highest rate of mortality. The pandemic greatly influences the management of chronic kidney failure and transplantation programs. This review describes clinical presentation and risk factors linked to COVID-19, the management and outcomes, COVID-19 vaccination in kidney transplant recipients, and the impact of COVID-19 on renal transplantation programs.

Key words: COVID-19, kidney transplantation, vaccination, outcome, SARS-CoV-2

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found to cause COVID-19 and has spread in waves throughout the world since the end of 2019. Until May 28, 2021, more than 168 million COVID-19 confirmed cases, 3.5 million deaths, and more than 1.5 billion doses of vaccine administered worldwide have been recorded (1).

Kidney transplant recipients (KTR) are considered to be at a high risk of COVID-19, with the worst outcome due to immunosuppression and clinical presentation that might differ from what is seen in the general population. This review mainly focuses on clinical presentation and risk factors of COVID-19 in KTR, immunosuppression management and outcomes, and the influence of the COVID-19 pandemic on renal transplant programs.

CLINICAL PRESENTATION AND RISK FACTORS

As in the general population, KTR with COVID-19 infection mainly present with fever and respiratory symptoms such as cough and dyspnea. In some kidney transplant patients, fever may be absent (2). More recently, multiple studies have elucidated that COVID-19 is a systemic disease often manifesting with gastrointestinal (GI) symptoms, liver injury, cardiac involvement, encephalitis, atypical stroke, and acute kidney injury (AKI), in addition to endothelial cell injury and coagulopathy, the likely mediators of multiorgan involvement (3). Symptoms such as cough, shortness of breath, myalgia, headache, sore throat, and GI symptoms are more common in KTR than the typical COVID-19 presentation. Additionally, several unreported symptoms such as chest tightness and pain, coryza, dehydration, conjunctivitis, dizziness, and weight loss appeared in the SARS-CoV-2 positive KTR. Non-white ethnicity, obesity, diabetes, and asthma/chronic pulmonary diseases are risk factors independently associated with COVID-19 disease in patients with kidney transplants and immunosuppression modulation (4). Other risk factors are advanced age, male gender, not to mention immunosuppression itself. The burden of comorbidities such as diabetes and hypertension, which are mostly reported as significant factors influencing the outcome of COVID-19, as well as smoking and cardiovascular disease further compromise outcomes in KTR with COVID-19 (2,3,5).

END-STAGE RENAL DISEASE AND COVID-19

End-stage renal disease (ESRD) is considered when chronic injury to the kidney leads to decreased functioning of the organ with a glomerular filtration rate (GFR) below 15 mL/min/1.73 m^2 (6). At this level, renal replacement therapy (RRT) with either peritoneal dialysis, hemodialysis, or kidney transplantation should be initiated. In a review study, Valeri reports an infection rate of COVID-19 between 11%-26% among patients with ESRD, with a mortality rate of up to 24%-27%, which is 6-7 times higher than the rate of 4% reported in the global population (7). Thus, given the immunocompromised nature of ESRD and the high comorbidity burden seen in patients with kidney failure, patients with ESRD are among the most vulnerable populations to COVID-19.

Similar to the general population, the most common presenting symptoms in ESRD patients remain fever and cough (8,9). In contrast, Ferrey *et al*. described an atypical presentation with symptoms of gastroenteritis in ESRD patients, which was similar to KTR (10). Adapa *et al*. report on acute kidney injury (AKI) to be an independent risk factor for mortality in COVID-19 patients, with an incidence of 3%-15%. In patients with severe infection requiring intensive care, the rates of AKI increased significantly from 15% to 50% (11). Another concern is the high incidence of AKI in patients infected with COVID-19 requiring hospital resources that strain intensive care units and ventilator capacity and renal replacement resources (7). In COVID-19 patients with severe AKI and with established ESRD, continuation of their RRT is vital for survival. It is recommended that healthcare personnel should follow what the Centre for Disease Control recommends for personal protective equipment and safety guidelines during their interactions with those patients to decrease the spread of infection and nosocomial acquisition in RRT centers (11).

It has been recommended that hospitalized patients with COVID-19 who experience any form of AKI should be followed up closely after discharge to assess the ongoing kidney function (12).

OUTCOMES OF COVID-19 IN KIDNEY TRANSPLANT RECIPIENTS

The mortality rate of COVID-19 in KTR is at least four times higher than in the general population (2). Elias *et al*. report a high mortality rate among KTR with COVID-19, fluctuating between 20% and 28% as compared with 1%-5% mortality in the general population (4). Coronavirus pandemic is too recent and currently, data on the clinical course, imaging features, and outcomes in KTR have not yet been fully elucidated. In a study on 12 patients, where ten were admitted to the intensive care unit, nine were intubated, eight died of severe COVID-19 pneumonia and acute respiratory distress syndrome (ARDS), and four were discharged after complete recovery, Abrishami *et al*. report that the most common pattern of lung involvement was bilateral involvement with a diffuse pattern and posterior segmental distribution. Ground glass opacity, a feature highly suggestive of COVID-19, was observed in all cases and consolidation in the majority of them (Figure 1).

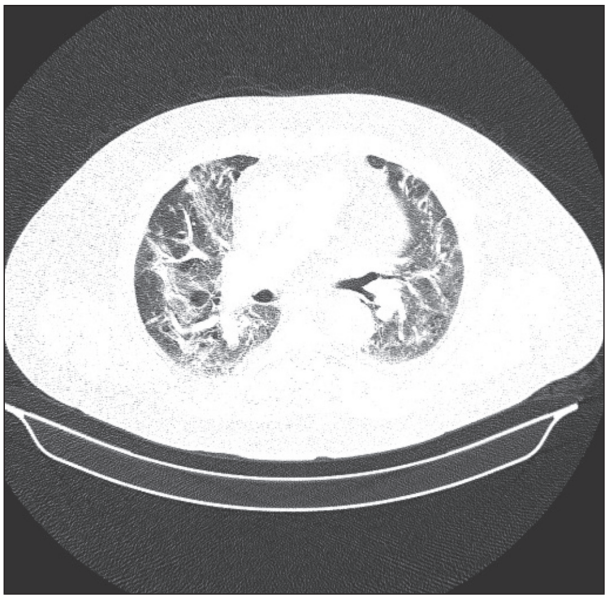

Fig. 1. *Chest computerized tomography in a renal transplant recipient with SARS-CoV-2 infection. Bilateral ground glass opacities with a diffuse pattern are present with areas of consolidation.*

The authors concluded that interlobular septal thickening, multilobar patterns, consolidative lesions, and a high score for lung involvement were more frequent among patients with poor outcomes and complicated cases with acute respiratory distress syndrome (ARDS) (13). Jawdeh reports an elevated incidence of AKI and a mortality rate of 13%-30%, which is higher than that in the general population (~5%). This could be attributed to the increased prevalence of comorbidities in addition to the immunosuppressed state leading to severe COVID-19 (3). Other studies have also found male gender to be associated with high mortality in COVID-19 infected KTR (3,14). Craig-Schapiro *et al*. also report that there was the need for RRT in hospitalized patients and that high inflammatory markers such as D-dimer, procalcitonin, and C-reactive protein were associated with high mortality (14). The management is mainly performed in patients presenting with severe symptoms such as dyspnea and

requiring mechanical ventilation, with immunosuppression reduction and supportive therapy in most patients (4,15).

MANAGEMENT OF COVID-19 IN KIDNEY TRANSPLANT RECIPIENTS

Immunocompromised patients, including those on immunosuppression following solid organ transplantation, are considered to be at a high risk of severe COVID-19. At this time, supportive care is paramount to combat this virus in solid organ transplant recipients. Little data are currently available regarding optimal medical management of KTR testing positive for SARS-CoV-2, including strategies for reducing or modifying immunosuppression. Elias *et al*. report that managing immunosuppression in patients with COVID-19 disease is arduous (4). Corticosteroids are a cornerstone of many immunosuppressive regimens; however, their use in SARS-CoV-2 remains controversial (4,16). Increased mortality recorded in transplant recipients with COVID-19 corroborates the role of diminished T- and B-cell immunity as a predisposing factor for severe infection. It would be reasonable to hold the antimetabolite in those with moderate disease and continue low-dose calcineurin inhibitor with or without glucocorticoids. In patients with severe disease and in critically ill patients, it may be justifiable to hold all maintenance immunosuppression except for steroids (3,17). Banerjee *et al*. suggest that antiproliferative agents (mycophenolate mofetil and azathioprine) be stopped at the time of admission to the hospital, the dose of prednisolone be either unchanged or increased, and tacrolimus dose be reduced. In severe infections (requiring intubation and ventilation), an argument can be made for stopping calcineurin inhibitors completely while maintaining corticosteroid therapy (5). This is in line with our approach that resulted in 7% mortality rate. An individual approach is mandatory with the decision based on disease severity, patient characteristics, and immunologic risk.

In a national survey in the United States, Boyarsky *et al*. report that antimetabolites were reported to have been stopped by 92.3% of respondents and calcineurin inhibitors were reduced by 26.9% of respondents (18). It has been reported that 81% of COVID-19 patients present with mild disease and can be managed at home. In contrast, severe and critical COVID-19 disease should be managed with prompt hospitalization while ensuring appropriate infection control and supportive care, with empiric treatment for bacterial infections, prevention of venous thromboembolism, and avoiding nebulized medications (2). Since patients should consider the risks and benefits of any treatment before giving their consent, the risks associated with minimizing or discontinuing immunosuppressants, thus potentially changing the fate of functioning kidney transplantation, should be clearly explained so that patients can make a well-informed decision (19).

INFLUENCE OF COVID-19 PANDEMIC ON RENAL TRANSPLANT PROGRAMS

The COVID-19 pandemic has pushed the world to rethink, reshape and adapt in the way everything works. Regarding renal transplant programs, the fear of allegedly increased susceptibility to infections in KTR due to immunosuppression has forced many centers to shut down their transplantation unit or change the paradigm and thus the routine of workflow. The reduction in transplantation volume during this time is partly due to concerns about the potential increased susceptibility and worsened outcomes of COVID-19 in immunosuppressed recipients (14). Loupy *et al*. report on strong association between rising coronavirus infections and marked reduction in the overall number of solid-organ transplantation, even in geographic regions with a low infection prevalence (20). In a national survey conducted in the United States linked to COVID-19 and transplantation, Boyarsky *et al*. report on complete suspension of living donor transplantations by 71.8%. However, most deceased donor programs in the United States continued to function with some restrictions (18), whereas in the United Kingdom, kidney transplant programs had to suspend temporarily both the deceased and living donor transplantation (21). The underlying reasons were to release/create more intensive care beds, liberate the workforce to support the intensive care unit, and, more importantly, prevent increase in mortality due to COVID-19 in immunosuppressed individuals (20). Concerning transplant procedures, SARS-CoV-2 infection could be missed in both donors and recipients who are asymptomatic, owing to the sensitivity issues in the RT-PCR test.

Additionally, in the immediate postoperative period and after hospital discharge, transplanted patients have increased susceptibility to SARS-CoV-2 infection due to induction therapy and immunosuppressive treatment (22). Until today, insufficient evidence is available to consider kidney transplantation as a safe procedure in COVID-19 pandemic areas. In emergencies, e.g., in cases of no vascular access, unfeasible dialysis, or a hyperimmune state, the benefits might outweigh the risks of kidney transplant (22). Kidney organs are not readily available and the number of patients on the waiting list keeps growing. All around the world guidelines are being set to increase the safety peri-, during, and post-transplantation procedures during the current pandemic, and specifically to avoid nosocomial COVID-19 infections.

The number of kidney transplantations in Croatia has dramatically decreased over the last year. Faced with the pandemic spreading in waves, the country has answered the epidemiologic challenges. However, the number of transplantations performed has fallen to the levels achieved during the war.

COVID-19 VACCINATION IN KIDNEY TRANSPLANT RECIPIENTS

The vaccine-preventable disease can cause adverse patient and allograft outcomes in KTR and live-attenuated vaccinations are contraindicated in KTRs due to the risk of infection (23). With the current COVID-19 pandemic, Ikizler *et al*. provide data suggesting that complete vaccination protocols should be implemented in patients receiving maintenance hemodialysis and in KTR (24). In the absence of confirmed association between natural SARS-CoV-2 infection and acute allograft rejection in KTR (25,26), it is unlikely that vaccine antigens would precipitate clinically significant immune responses to renal allografts. Thus, recommendations are to administer SARS-CoV-2 vaccine pre-transplantation when possible or at least at 3 months post-transplantation. Nevertheless, future evaluations of SARS-CoV-2 vaccine platforms in KTR must confirm their safety and immunogenicity (25). Considering only humoral response, Cucchiari *et al*. report that S-specific antibodies were developed only by 29.9% of patients in their study population (27). Grupper *et al*. report on a 37.5% antibody response rate after the second dose of the BNT162b2 (Pfizer) vaccine (26). Boyarsky *et al*. have recently reported a higher seroconversion of 54% in patients receiving an mRNA-vaccine, either mRNA-1273 (Moderna) or BNT162b2 (Pfizer) (28). Considering the percentage of patients who had positive S-ELISpot after the second dose, the percentage of patients who developed either humoral or cellular response increased to 65% and half of the antibody-negative patients had developed positive ELISpot. This finding highlights that patients may be protected against SARS-CoV-2 despite the absence of S antibodies (27).

We were the first to report COVID-19 in patients who had completed the vaccination program (29-31), indicating a high risk of nonresponding to the vaccination.

CONCLUSION

Kidney transplant recipients remain a population at risk of COVID-19 infection due to their immunosuppression status, high morbidity and mortality. All over the world, the pandemic of COVID-19 has forced transplant programs to either shut down or to readapt. Vulnerable KTR patients who are not yet vaccinated or are non-responsive to mRNA vaccines should be closely followed up and sanitary protection measures strictly respected.

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SAŽETAK

PANDEMIJA COVID-19 I TRANSPLANTACIJA BUBREGA

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Infekcije su česta komplikacija nakon transplantacije bubrega. Povezane su s visokom stopom pobola i smrtnosti. Od samog početka pandemije COVID-19 uočeno je da bolesnici s transplantiranim bubregom imaju lošije ishode i višu stopu smrtnosti u usporedbi s općom populacijom. Pandemija COVID-19 je značajno utjecala na zbrinjavanje bolesnika sa završnim stadijem kronične bubrežne bolesti i na transplantacijske programe. Prikazujemo klinički nastup, čimbenike rizika, liječenje i ishode COVID-19 u populaciji bolesnika s transplantiranim bubregom, kao i utjecaj pandemije na transplantacijske programe.

Ključne riječi: **COVID-19, transplantacija bubrega, cijepljenje, ishodi, SARS-CoV-2**