COVID-19 IN RENAL-TRANSPLANTED RECIPIENTS: A NARRATIVE REVIEW

Covid-19 em pacientes transplantados renais: uma revisão narrativa

Suellen Rodrigues Martins[*a], Lorraine Vieira Alves*[*a], Marta Lamounier Moura Vargas Corgozinho[a]; Jenner Karlisson Pimenta dos Reis[b], Bruno Eduardo Fernandes Mota[a], Kátia de Paula Farah[c], Karina Braga Gomes[a], Luci Maria Santana Dusse[a], Patrícia Nessralla Alpoim[a], Ana Paula Lucas Mota[a]*

ABSTRACT

COVID-19 is an emerging disease mainly associated with Severe Acute Respiratory Syndrome (SARS). This disease causes a cytokine storm release in response to viral infection, and can lead to several systemic complications. Acute kidney injury (AKI) is one of these complications and renal replacement therapy may be necessary for the infected patient. In this context, renal-transplanted recipients (RTR) and patients with chronic kidney diseases are in the risk groups for COVID-19 due to their increased inflammatory state and endothelial dysfunction. Furthermore, maintenance immunosuppressive therapy in RTR can also be another complicating factor, since it influences the response from the immune system against pathogens, including SARS-CoV-2. However, it is believed that the worst outcomes of COVID-19 are mainly caused by an exaggerated inflammatory response than to the direct virus action; therefore, in a hyper-inflammatory state, immunosuppression therapy could be beneficial. This narrative review aims to present the main clinical and laboratory findings of 22 studies involving RTR affected by COVID-19. This review can contribute to the management of COVID-19 and its consequences in this risk group.

Keywords: Communicable Disease; Coronavirus Infections; Renal Insufficiency; Kidney Transplantation.

Institution:

[1] Federal University of Minas Gerais, Belo Horizonte, Minas Gerais (MG), Brazil.

[1a] Department of Clinical and Toxicological Analysis, Faculty of Pharmacy

[1b] Department of Preventive Veterinary Medicine, Faculty of Veterinary Medicine

[1c] Department of ClinicalMedicine, Faculty of Medicine

**Authors contributed equally to this work.*

Correspondence:
Ana Paula Lucas Mota
analucasmota@gmail.com

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INTRODUCTION

The World Health Organization (WHO) declared a new pandemic in March 2020, which started on December 12th, 2019, in Wuhan, an important trade center in China.[1] The etiologic agent, isolated from airway epithelial cells of patients with unusual pneumonia was named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), formerly called HCoV-19, and the disease was designated as Coronavirus Disease 2019 (COVID-19). This virus mainly affects the respiratory systems and can be related to fatal pneumonia. It also affects gastrointestinal and central nervous systems. In addition, it can alter liver and kidney function.[2-4]

SARS-CoV-2 can be transmitted among humans via airborne route. In the last months, the amount of COVID-19 cases has increased exponentially, and the infection has spread rapidly around the world, appearing to be more contagious, but less fatal than Middle East Respiratory Syndrome-Coronavirus (MERS-CoV), the coronavirus that caused another pandemic in the past.[5] Of note, the COVID-19 has been associated with high morbidity in elderly and comorbid individuals. Therefore, preventive measures of social isolation and educative practices have been set up to prevent a collapse of health care centers around the world.[6]

From epidemiological data collected in many countries affected by COVID-19, it has been observed that all ages are susceptible to the COVID-19 infection. Until now, ages of 65 and above (elderly people) is one of the major risk factors. Moreover, other high-risk factors to develop severe illness of COVID-19 include long-term residents of nursing homes; immunocompromised persons; bearers of chronic lung and cardiovascular diseases; severe obesity (body mass index [BMI] >40), diabetes, renal failure or liver disease.[7]

More than 157 million COVID-19 cases have been confirmed worldwide, totaling almost three million deaths. United States of America remains the most affected country, with the highest number of COVID-19 cases and deaths in the world. In Brazil, the first case was diagnosed on February 26th, 2020, also considered the first case in Latin America. Currently, 440 days after the first diagnosis, Brazil is the country with the second-highest number of deaths and the third-highest number of confirmed cases in the world. Moreover, due to the territorial extension and lack of diagnostic tests, underreported cases cannot be ruled out. Suspected cases and deaths of COVID-19 have been reported, but only when associated to respiratory syndromes, such as pneumonia and respiratory failure. Severe cases involving other organs are not included in the general statistics.[8,9]

According to recent publications, the number of renal-transplanted recipients (RTR) affected by COVID-19 still corresponds to a small portion in the world population. Worldwide data on cases and number of deaths of these patients are not yet available. It is important to note that most viral infections are not self-limiting in immunosuppressed patients as RTR, because the use of immunosuppressive agents can cause dysfunction in the immune surveillance system, and consequently, a higher susceptibility to viral infections, such as Cytomegalovirus, Epstein-Barr virus and BK polyomavirus.[10] In addition, for being more susceptible to viral infections, these patients also have several comorbidities, such as diabetes mellitus and cardiovascular disease, which are associated with more severe cases of COVID-19. Clinical signs and symptoms, as well as the treatment and prognosis of COVID-19 in this group of patients may differ from the general population, and the alternative treatment methods deserve considerable attention.[1,4,11,12]

METHODS

The literature review was performed by using the PubMed database. The inclusion criteria were publications that included RTR with COVID-19 published until May 9, 2020. Review articles and articles which did not include renal-transplanted patients were excluded. The search terms were: COVID-19; SARS-COV-2; Renal Transplantation and Kidney Transplantation. Twenty-two studies were included in this analysis,[13-34] which consisted of cases reports (N=12),[18,19,23-25,27-31,33,34] letters (N=6),[13-15,20,26,32] retrospective study (N=1),[22] rapid communications (N=1) [21] and special reports (N=2).[16,17] The studies assessed amounted 167 RTR.

Descriptive literature review

The main clinical and laboratory findings of RTR diagnosed with COVID-19 are presented in Table 1. Among the 167 RTR described, 115 were male, aged from 29 to 77 years old. Most RTR were on triple maintenance immunosuppression that included a calcineurin inhibitor (CNI) (tacrolimus - TAC or cyclosporine - CsA); antimetabolite (mycophenolate mofetil - MMF or mycophenolate sodium - MPS) and corticosteroid (prednisone - PRED), and the majority received the renal graft from deceased donors.

The main initial signals and symptoms were fever;[14,16-34] respiratory symptoms (e.g. cough;[14,16-22,24-26,28-34] dyspnea;[14,15,17-21,24,26,28,32,34] shortness of breath;16,[17,22,29,30] rhinorrhea [18,23]); myalgia;[14,17,20,21,32] gastrointestinal symptoms (e.g. diarrhoea;[13,14,16,19-22,32] vomiting;[16,18,19,27,33] nausea;[18,19,27,34] and loss of appetite [27,30,34]). Hemoptysis;[18,21] headache;[18,34] emesis;[21] conjunctivitis;[33] dizziness;[27] high blood pressure[33] and mild dehydration [33] were reported as uncommon signals and symptoms associated to SARS-CoV-2 infection.

A large-scale laboratory investigation was carried out among the RTR described in the studies. Assessment of inflammatory, renal and hematological biomarkers was most commonly requested. A likely pro-inflammatory profile was observed with high levels of C-reactive protein (CRP);[14,16-18,21-26,28,30,32-34] interleukin 6 (IL-6);[20,21,24,26,31,32,34] ferritin;[15-17,20,21,24] lactic dehydrogenase (LDH);[14-16,18,20,21,24,31,32] procalcitonin (PCT);[17,21,24,33] and erythrocyte sedimentation rate (ESR).[18,21,28,34]

A possible liver injury assessed by transaminases was detected in six studies.[16,18,22,24,28,30,34]

As in the general population with COVID-19, the presence of lymphopenia was the most common hematological finding [14,16,18-31,33,34] and the lower CD4+ and CD8+ count [20,24,29] was associated to severe forms of COVID-19 in RTR. Thrombocytopenia was also considered another common finding in this group.[20,24,25,27,33]. Few studies reported decreased red blood cell count [25] and haemoglobin levels.[25,33] The presence of hypercoagulable status was also reported, assessed by prothrombin time;[24] fibrinogen [30] and D-dimer levels.[14-17,20,28,32,33]

Most RTR evolved with decreased renal filtration function, assessed by creatinine plasma levels;[15-19,22,24,25,27,28,30,32,33] blood urea nitrogen;[15,30] estimated glomerular filtration rate (eGFR) [16,24,33] and urinary markers (e.g. oliguria;[15,27] anuria;[16,28] proteinuria [18,24,28,34] and hematuria).[27]

Different pharmacological therapies were prescribed in the studies: hydroxychloroquine (or chloroquine);[13,14,17,19-21,24,32,33] antiretrovirals (lopinavir + ritonavir;[13,14,17,18,27,31-33] oseltamivir; [16,23-25,28,29] darunavir; [17,32] umifenovir;[30,34] ribavirin.[30]); antibiotic therapy (azithromycin; [13,14,19-21,33] cephalosporins;[14,17] ceftaroline;[24,33] moxifloxacin;[25,27,29,30,34] ceftriaxone;[18,19,24,31,33] biapenem; [34] meropenem [33]); glucocorticoids (prednisone – PRED;[19,20,24] methylprednisolone (MP);[14,15,17,22,25,28-30,34] Dexamethasone [17]) and Intravenous immunoglobulin (IVIG).[14,22,25,28,30,34] Two studies reported the use of prophylactic anticoagulation.[14,30] Blood transfusion was required in patients from two studies.[16,25]

The immunosuppression protocol for allograft maintenance was modified or discontinued in most cases due to possible pharmacological interactions, and as an alternative to recover the low lymphocyte count. Only eight studies did not change the immunosuppressive protocol.[16,21-24,27-29,31]

As reported to the general population with COVID-19, pneumonia and acute respiratory distress syndrome (ARDS) were the main complications among RTR,[13-18,20-22,24,25,27-30,32-34] followed by acute kidney injury (AKI),[14-17,19,21,28,32] allograft loss,[13,22] and allograft rejection.[25]

Several patients required renal replacement therapy (RRT);[14-17,20,21] intensive care unit (ICU)[13,16-18,30,33] and supplemental oxygen.[13,15-22,24,29,30,32-34] Laboratory data from one RTR showed severe bone marrow suppression [25] and two patients developed anaemia.[25,30] Other three studies reported the occurrence of liver damage among RTR.[22,27,32] Twenty-nine RTR died (17,4%)[13,14,16,17,20-22,29,32] due to progressive respiratory failure;[13,14,17,20-22,32] multiorgan failure [29] and probable sepsis.[16,17]

The descriptive analysis of the clinical course of the patients was possible in 18 articles,[15,16,18,19,21-34] a total of 52 patients, comprehending the management of mild and severe forms of the disease. A mild course without complications, with discharge or no hospitalization, was observed in nine patients.[16,21,23,31] Among these, there was no change in the immunosuppressive therapy; in four patients,[16,21,23,31] the antiproliferative medication (MPA or MMF) was interrupted in three,[21] all immunosuppression (TAC and MPA) was withdrawn in one [21] and leflunomide was removed in only one case.[21] For the nine patients with a mild course of the disease, two patients did not use any anti-COVID-19 therapy [16, 21], hydroxychloroquine + azithromycin were administered in two patients,[21] only hydroxychloroquine in three,[21] oseltamivir in one [23] and lopinavir/ritonavir were given to one patient.[31] Only one patient did not show complications, but he was not discharged. This patient was treated with hydroxychloroquine + azithromycin, and MMF therapy was discontinued.[21]

From the 52 patients, seven did not die but had a severe course of the disease that required intubation. Of these, one had the dose of TAC reduced;[15] one had the dose of everolimus (EVE) reduced at ICU admission that was discontinued late added to the inclusion of CsA;[18] one had a reduction in the PRED and TAC doses [21] one had MMF discontinued;[21] two had TAC and MMF discontinued,[16,21] with maintenance [16] or inclusion [21] of PRED; and in one patient, TAC and EVE were held, only maintaining PRED.[33]

Treatments were very different among severely ill patients. Most received hydroxychloroquine, with one patient receiving only that drug;[21] two receiving hydroxychloroquine + azithromycin, with the inclusion of tocilizumab [21] or lopinavir/ritonavir;[33] one received chloroquine + lopinavir/ritonavir;[18] one received MP;[15] and one oseltamivir.[16]

Only one of the critically ill patients was not treated with any anti-COVID-19 therapy.[21] Only one patient with severe disease was discharged. This patient was treated with chloroquine + lopinavir/ritonavir.[18] In addition, only one patient was extubated and his treatment included hydroxychloroquine + azithromycin and tocilizumab.[21] By the end of the follow-up, none of these patients had died and all but one remained hospitalized.[15,16,18,21,33]

Only three patients needed to be admitted in the ICU, but they neither were intubated nor died. Of these, MMF was discontinued, and no antiviral therapy was used in 2 patients;[16] and in 1 case, all immunosuppressant was withdrawn and treatment with umifenovir, ribavirin, MP and IVIG was included.[30]

Of the 52 patients described, only six died.[16,21,22,29,32] Unfortunately, due to incomplete or grouped data presentation, it was not possible to collect the data from each deceased RTR. Of the six patients who died, five had fever and cough.[16,21,22,29,32] The lymphopenia [16,21,22,29] and increased levels of CRP [16,21,22,32] were found in five patients and high levels of LDH in four.[16,21,32] These findings were the most common laboratory data in the deceased patients. Immunosuppressive therapy was not withdrawal in only one RTR. Besides, this patient had severe complications such as multiorgan failure (lung, kidney and heart).[29] The discontinuation of MMF or MPA occurred in five RTR [16,21,22,32] and the withdrawal of CNI (TAC) in three.[16,22,32]

Regarding anti-COVID-19 therapy, hydroxychloroquine was used by half of the RTR who died,[21,32] combined with azithromycin [21] or with lopinavir/ritonavir.[32] One patient was treated with oseltamivir, lopinavir/ritonavir and MP,[29] one was treated with unspecified antiviral therapy [22] and one patient did not receive any specific antiviral drugs.[16] The most relevant finding was severe renal impairment in all deceased RTR, such as AKI [16,21,32] or acute allograft failure.[22] Furthermore, five patients had a respiratory impairment, requiring mechanical ventilation.[16,21,22,29,32]

It is important to highlight that the 52 patients analyzed had a pro-inflammatory profile with increased systemic inflammatory markers. The most common findings were high levels of CRP in 40 patients,[16,18,21,22-26,28,30,32-34] and high levels of LDH in 18 patients.[15,16,18,21,24,28,31,32] High levels of IL-6 were also found in 12 patients.[21,24,26,31,32,34] In addition, increased ferritin levels were detected in 11 patients.[15,16,21,24]

DISCUSSION

Patients with chronic kidney disease (CKD) and RTR are more susceptible to COVID-19 poor outcomes than other individuals without renal disease. In this review, among the 167 RTR described, 29 died (Table 1) representing 17.4% fatality rate. This rate is much higher than the estimated rate for the general population, which currently ranges between 5% and 6%.[35,36]

In our review, the descriptive analysis with the presentation of the clinical course was possible in 52 patients.[15,16,18,19,21-26,28,30-34] Comparative analysis between the six patients who died showed the presence of some common factors, such as the male gender, advanced age, a long post-transplant time, presence of lymphopenia, pro-inflammatory profile, and impairment of renal or respiratory function.[16,21,22,29,32] These variables have already been described as higher risk factors to develop clinical severity in patients with COVID-19.[7] It is important to mention that the comparative analysis for all RTR (N = 167) was not possible due to the absence of individual data for the RTR in several studies.

Serious complications of COVID-19 occur due to comorbidities, in particular hypertension and diabetes, and in the RTR because of residual CKD and long-term immunosuppressive treatment. SARS-CoV-2 infection can be more severe in these patients and intensive care hospitalization may be necessary.[12] The case reported by Zhu et al., 2020 [22] showed the influence of several comorbidities (mainly, hypertensive heart disease and chronic obstructive pulmonary disease) on the clinical evolution of a 59 years-old RTR diagnosed with COVID-19 who died (Table 1). Unfortunately, the comparative assessment of COVID-19 clinical course based on comorbidities was not possible due to very limited and missing data in some included studies.

Signs and symptoms of COVID-19 in RTR were similar compared to the general population with the infection.[1,7] However, less common symptoms were described in several RTR, such as conjunctivitis, loss of appetite, headache, intermittent abdominal pain, mild dehydration, high blood pressure and dizziness (Table 1) that can lead to late diagnosis with consequently worse outcomes. As expected, pneumonia and ARDS were the most common complications (Table 1).

Recent studies have shown a lower incidence of AKI (3-9%) in patients infected with SARS-CoV-2.[37-39] Despite the lower rate of renal injury, patients with COVID-19 have shown a high frequency of changes in renal parameters, such as albuminuria, proteinuria, uremia and hematuria, along with a reduction in renal density, suggestive of inflammation. An increase in the creatinine plasma levels can also be found.[35,40] These laboratory changes were also present in the RTR, especially among those who developed AKI or allograft loss. Unlike findings in the general population with COVID-19, we found AKI and renal graft loss as frequent complications in the studies assessed, mainly among RTR who died.[16,21,32] Renal impairment observed in SARS-CoV-2 could be explained due to the interaction of SARS-CoV-2 with angiotensin-converting enzyme 2 (ACE2) receptors in tubular renal cells.[16]

Most RTR who died developed dyspnea and gastrointestinal symptoms (main diarrhea) as initial presentation, which could be related to prolonged use of the immunosuppressive therapy (Table 1).

In the present review, the total 52 RTR analyzed showed a pro-inflammatory profile with high levels of CRP, LDH, IL-6 and ferritin.[15,16,18,21-26,28,30-34]

The presence of lymphopenia, high levels of D-dimer, ferritin and CRP were also common findings among RTR with worse outcomes (Table 1). Banerjee et al. (2020)[16] suggested a possible occurrence of microvascular thrombosis or disseminated intravascular coagulation in the RTR with COVID-19. This fact could intensify the pro-inflammatory state and worsening of the clinical evolution. Thus, the assessment of these laboratory markers could be a promising prognostic tool.

Noteworthy, the immune response against SARS-CoV-2 in RTR is different when compared to patients without pre-existing health conditions, requiring more attention.[22] The cell-mediated immune response is crucial to hold the progression of COVID-19 to more severe stages. However, the long-term use of immunosuppressive agents by RTR can affect the T-cell immune response leading to suppression of the immune system.[41] Thus, in individuals with impaired immune responses such as RTR, SARS-CoV-2 is capable of causing massive tissue damage, especially in the kidney, due to the high expression of ACE2 in this organ. Concomitantly, cell death caused by the viral infection leads to innate immune response mediated by macrophages and granulocytes. This process causes even more damage to the organs, requiring efforts to control the immune response.[42] In addition to this effect, the release of the cytokines may be present in severe conditions of COVID-19. Thus, pro-inflammatory cytokine blockade, especially IL-6, TNF and IL-1, appears to be beneficial for patients with severe forms of COVID-19.[43]

It is important to highlight that temporary reduction or discontinuation of immunosuppressive therapy promotes the recovery of the immunity necessary to control the viral infection and minimize the progression of COVID-19. Such practice is already common for other virus infections and at the end of the disease, the immunosuppressive agents are gradually reintroduced.[22,44,45]

Management of immunosuppressive therapy in RTR is different between studies (Table 1). It is essential to maintain medications that inhibit the process of kidney damage and the inflammatory response linked to the cytokine storm, in order to prevent severe cases of COVID-19. It is already known that immunosuppressive therapy, especially CNI impairs the response of T cells, leading to invasion and uncontrolled spread of the virus. In RTR with COVID-19, CsA could perhaps be chosen instead of TAC, since its chemical derivatives decreased the expression of a human coronavirus protein in vitro.[46,47] In our review, CsA was included in the immunosuppressive regimen of a patient with severe disease who was discharged.[18]

Based on the systemic viral infection, maintenance of CNI and glucocorticoids, as well as the withdrawal of antiproliferative drugs may be recommended for mild cases of RTR with COVID-19, because the last drugs limit the T and B cell proliferation and can suppress the bone marrow, inducing significant leukopenia, the most common finding in patients with COVID-19. On the other hand, in severe cases, the immediate withdrawal of antiproliferative drugs and CNI, and an increase of the glucocorticoid doses may be recommended.[46,48] In the present review, none of the patients dead or alive with severe illness, including those admitted to the ICU had their dose of PRED increased.[15,16,18,21,22,29,30,32,33] Only one patient with a severe course of the disease who did not die had PRED added to the immunosuppressive regimen.[21] In contrast, one patient had a reduced dose of PRED[21] and one patient had this immunomodulatory agent suspended.[30] However, the withdrawal of the CNI and antimetabolite [16,21,22,30,32] or the suspension/reduction of

one of these agents [15,16,21] also occurred in patients with severe clinical evolution. These findings were similar to the protocol recommended.[46,48] However, it remains unclear what is the best option to not impairing the immune response of the host and helping to hold the SARS-CoV-2 with no kidney injury.

Although there is no specific treatment for SARS-CoV-2 in general and no conclusive evidence for the treatment and management of immunosuppressive agents in RTR, we observed some patterns in the studies. Most patients with a mild course of the disease had no change in immunosuppressive therapy [16,21,23,31] or had their antiproliferative agent discontinued.[21] A Spanish group of Hospital de la Paz recommended a protocol with no changes in the immunosuppressive therapy for young patients without pulmonary infiltrate. In the case of elderly patients, the group recommended the suspension of the antiproliferative agent and the maintenance of CNI and corticosteroids.[49] The protocol of the Spanish group was very similar to the protocols analyzed in this review. All patients in the present review with a mild course who did not show changes in immunosuppressive agents were young with no pathological findings on chest X-ray (CXR) and chest computed tomography (CT) scan.[16,21,23,31] In the Spanish protocol, the authors suggested the discontinuation of antimetabolite and CNI agents (for CNI, only a few days, if there is clinical improvement) for patients with pulmonary infiltrates.[49] Similarly, patients with a mild course who showed findings of pulmonary involvement had their antimetabolite suspended.[21]

The removal of all immunosuppressant and the maintenance or addition of corticosteroid was the most frequent protocol in severe cases of COVID-19 with no deaths.[16,21,33] Despite the uncertainties, this protocol is well accepted, since the continuation of a corticosteroid can provide immunological protection of the renal allograft and the maintenance of the homeostasis. The immunosuppressant acts as anti-inflammatory and immunomodulatory agent, controlling the dysregulation of immunological markers in SARS-CoV-2 infection, in addition to maintaining the permeability and integrity of the endothelium.[50,51]

The scientific community around the world has proposed several empirical treatments for COVID-19. The treatment is normally based on the potential activity of the drug, such as antiviral activity or anti-inflammatory and/or anticoagulant effects. There are hundreds of drugs under investigation. Based on the studies analyzed in this review, the most prescribed medicines against SARS-CoV-2 were hydroxychloroquine and lopinavir/ritonavir (Table 1). Hydroxychloroquine and chloroquine were, at first, considered potential drugs, especially in severe cases of the disease. However, these drugs could cause cardiovascular risk, especially when combined with the antibiotic azithromycin, which also prolongs the QT interval. In addition to not being safe, these drugs have not been shown to be effective in preventing or treating COVID-19.[52]

In our study, it was possible to analyze the course of the disease in 52 RTR, in which nine patients with mild clinical course without complications, with discharge or with no hospitalization, seven with severe course of the disease, requiring intubation, and six patients who died. Most mild cases used hydroxychloroquine as a single therapy or combined with azithromycin.[21] The majority of critically ill patients (without death) also used hydroxychloroquine, either as a single therapy [21] or in combination with azithromycin + tocilizumab [21] or lopinavir/ritonavir.[33] The use of hydroxychloroquine was also present in half of the cases in which patients died.[21,32] These findings showed that the use of hydroxychloroquine was prevalent in renal-transplanted patients included in the present review. However, the FDA has already revoked emergency authorization for the use of hydroxychloroquine and chloroquine in the treatment of certain hospitalized patients with COVID-19, when a clinical trial is not available or patient participation is not feasible. According to the FDA, the basis for such revocation is a series of studies that have demonstrated the ineffectiveness of hydroxychloroquine in killing or inhibiting the virus, as well as in decreasing the likelihood of death or in accelerating recovery in patients infected by SARS-CoV-2.[52]

Other treatments, such as remdesivir that blockades an important viral enzyme, lopinavir/ritonavir and interferon-β1a are being tested to inhibit viral activity and control inflammation.[46] In our review, two patients who died were treated with lopinavir/ritonavir combined with other therapies.[29,32]

The use of monoclonal antibody, tocilizumab, which competitively inhibits the binding of IL-6 to its receptor, is another supportive treatment when a significant increase in IL-6 levels is detected.[53] This increase is associated to the cytokine storm and may be associated to severe forms of COVID-19.[54] In this review, the use of tocilizumab was described in some studies.[13,14,17,20,21] Tocilizumab was administered together with hydroxychloroquine and azithromycin in a young RTR with a severe clinical course. The patient remained

hospitalized but was extubated, showing improvement in the clinical outcome.[21]

Other treatments for COVID-19, such as the use of convalescent plasma and immunoglobulins, passive immunotherapies, may be related to the reduction of viremia by mechanisms linked to viral neutralization, antibody-dependent cell cytotoxicity and phagocytosis by immune cells.[55,56] A recent study used convalescent plasma transfusion as an alternative treatment in critically ill patients. In this study, despite the limited sample size, an improvement in clinical outcome was observed.[57]

In addition to the uncertainties about the best antiviral therapy, as well as the best management of immunosuppressive therapy, it is important to mention that the dynamics of the dialysis centers and the performance of the transplant have also changed. The current pandemic has caused changes and adaptations in the most diverse areas, aiming to reduce the risk of infection and to spread SARS-COV-2. Clearly, this is the most relevant health problem and perhaps the most significant economic problem suffered by humanity in recent years. This situation has directly affected the dialysis centers, organ uptake and transplantation.[58]

Due to the high incidence of COVID-19 in Brazil, the Brazilian Organ Transplant Association (ABTO) detected a reduction in the transplant surgery in the last quarter. It seems to be more pronounced in the coming months. There was a sharp drop in transplants with a living donor (30%), probably to avoid the risk of acquiring COVID-19 during hospitalization and the surgical procedure.[58] The ABTO released recommendations to improve donor and recipient management for kidney transplantation surgery, such as COVID-19 laboratory test for asymptomatic patients; disregard transplantation surgery for positive cases; to perform the transplantation in suspected clinical cases based on risk-benefit; to reduce the people flow in the transplant centers, avoiding unnecessary visits and companions.[59] It is worth highlighting the importance of maintaining transplantation surgeries as much as possible, in order to avoid the accumulation of patients on the waiting list, and exposing the patient to a relevant risk of viral spread in dialysis centers.[58,60]

Renal disease increases the risk to develop severe COVID-19 infection, and hospitalized kidney transplant recipients infected with SARS-CoV-2 have shown a high mortality rate (20-30%). Randomized controlled trials have been performed to determine which drugs are beneficial in the treatment of COVID-19. However, none of them included RTR. Thus, the management of the transplanted population continues to be based on the transplant centers experience, as well as on clinical judgment and limited evidence from studies and case reports that included RTR.[61,62]

No association between vaccines available in the world and transplant rejection has been identified so far. In immunosuppressed patients, a decrease in the immunogenicity of the SARS-CoV-2 vaccine is expected and lower rates of seroconversion have been found in these patients compared to immunocompetent individuals. However, despite the weak antibody response, the immunization of the immunocompromised group, such as RTR, is a strategy to prevent and to reduce the severity of COVID-19 in this population, decreasing its morbidity and mortality. Close surveillance of RTR and other immunosuppressed patients should be performed after vaccination and strategies such as additional booster dose or respiratory mucosal vaccination can be adopted in cases of weak anti-SARS-CoV-2 antibody response. Prevention strategies for COVID-19 are particularly important in this group of patients, since the immunocompromised state can accelerate the SARS-CoV-2 viral evolution and, consequently, cause the formation of new variants, affecting SARS-CoV-2 virulence and transmissibility. [62-66]

In summary, renal-transplanted patients are a group highly affected by the pandemic situation. More studies with RTR are needed to understand what is the best clinical management for these patients in order to reduce death and prevent renal allograft loss.

CONCLUSION

The presence of SARS-CoV-2 infection in renal-transplanted patients requires more attention due to atypical presentations and worst outcomes, especially in elderly patients, with a significant reduction of T cells, reflecting the intensity of immunosuppression. The withdrawal of specific immunosuppressive agents could contribute to an increase of the natural immune response against SARS-CoV-2, besides a potential reduction of pharmacological interactions between the therapies. The deaths of RTR can be proportionally significant, especially when compared to the outcome of the general population with COVID-19. It may be necessary to reassess the screening protocols to propose better management for renal-transplanted patients with COVID-19. These issues should be further explored in future research.

***Table 1** – Main clinical and laboratory findings of RTR diagnosed with COVID- 19*

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
Montagud-Marrahi, E. et al., 2020 [13]	Lettertothe Editor	33 RTR; (male =57.6%; mean age = 57.3 years old) post-transplant timemedian = 10.7 (4-14.7 years)	Diarrhoea(-)	-	Pneumonia (73%), renal graft loss (3%). 13 patients (52%) required ICU admission(6% with mechanical ventilation)	(Outpatients =7) Azithromycin (2); Azithromycin+Hydroxy-chloroquine (1) **(Inpatients = 26)** Lopinavir/Ritonavirazithromycin and hydroxychloroquine combination, (21); Azithromycin+ Hydroxychloroquine (1); Hydroxychloroquin (2); Azithromycin (1); Tocilizumab (13); Interferon Beta (13); Anakinra (3)	In all patients, MMF and mTORi were temporarily withdrawal; and CNI was withdrawal if Lopinavir/ Ritonavir was prescribed; PRED as maintenance immuno-suppression	2 patients died; 21 patients were discharged to home and 10 were discharged to the adapted hotel to reduce hospital pressure
Trujillo, H. et al., 2020 [14]	Research Letter	26 RTR (male = 12 (46%); mean age = 61 (±14) years old	Fever (12), non-productive (17) and productive cough (6), dyspnea (15), gastrointestinal symptoms (10), asthenia/ myalgia (4)	High levels of CRP, D-dimer and LDH; lymphopenia. Glass opacities, alveolar consolidations and bilateral pulmonary involvement on CXR	ARDS (10), AKI, pneumonia. 9 of RTR required RRT	MP (12); Hydroxychloroquine (22); Cephalosporines (14); Carbapenem (11); Azithromycin (-); Linezolid (-); Lopinavir/ ritonavir (7); Tocilizumab (5); IVIG (-); Prophylactic anticoagulation (Heparin) (-)	TAC (-);MMF (-) and mTORi (-) withdrawal	06 patients that developed ARDS died (23%);7 RTR were discharged from hospital
Billah, M. et al., 2020 [15]	Lettertothe Editor	44-year-old male (84 months post-transplantation)	Dyspnea	High levels of BUN, Cr, ferritin, LDH, D-Dimer, phosphorus, and potassium, oliguria, urine output decreased, azotemia Multifocal opacities on CXR	AKI, hyperkalemia. Required RRT (hemodialysis). Intubated for respiratory failure.	MP/ Sodium zirconium cyclosilicate; Loop diuretics	TAC dose reduced	The patient remains ventilator dependent and in dialysis treatment
Banerjee D. et al., 2020 [16]	Special report	48-year-old male (372 months post-transplantation)	Cough, fever and mild shortness of breath	-	No complications (clinically well)	-	Unchanged	Stayed at home (fully recovery)
		67-year-old female (14 months post-trans-plantation)	Cough, fever and shortness of breath	High levels of CRP, LDH, D-dimer, serum troponin I and Cr, normal total white cell count, and mild lymphopenia. Bilateral patchy consolidation on CXR	AKI; ARDS; severe metabolic acidosis resistant. She required ICU, noninvasive ventilation and subsequent intubation with ventilation. She needed CVVH	No specific antiviral drugs; Broad-spectrum antibiotics	TAC and MMF withdrawal	Dead (possible cause: bowel infarction or sepsis)
		54-year-old female (5 months post-transplantation)	Shortness of breath	High levels of CRP and Cr, anuria. Bilateral Pulmonary infiltrates on CXR	AKI, ARDS, pneumocystis. She needed CPAP therapy. She required posterior intubation with be ventilation. She needed CVVH	Oseltamivir; Broad spectrum antibiotics/ Cotrimoxazole	TAC and MMF withdrawal	Remains inpatient (remained under ventilation)
		65-year-old male (21 months post-transplantation)	Shortness of breath and chest pain	-	He was admitted to ICU, required oxygenation support	-	MMF withdrawal	Remains inpatient (in medical ward with stable kidney function)

Table 1 – *Main clinical and laboratory findings of RTR diagnosed with COVID- 19 (cont.)*

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
Banerjee D. et al., 2020 [16]	Special report	65-year-old male (21 months post-transplantation)	Shortness of breath and chest pain	-	He was admitted to ICU, required oxygenation support	-	MMF withdrawal	Remains inpatient (in medical ward with stable kidney function)
		69-year-old female (3 months post-transplant -ation)	Shortness of breath, fever, diarrhoea, and vomiting	Lymphopenia, high levels of NT-proBNP. Shadowing of left base on CXR	AKI. She required ICU, oxygenation via nasal cannula and blood transfusion	Doxycycline; Piperacillin-tazobactam/ Paracetamol; Furosemide	MMF withdrawal	Remains as inpatient (in medical ward)
		54-year-old male (84 months post-transplant -ation)	Cough and fever	High levels of Cr	AKI	- /Paracetamol	MMF withdrawal	Stayed at home (still has symptoms)
		45-year-old male, 32 months post-transplant -ation)	Fever, flu-like symptoms, cough, and shortness of breath	Lymphopenia, high levels of CRP, ferritin, D-dimer, LDH, ALT and troponin I, low eGFR, normal haemoglobin, normal white cell count. Bilateral infiltrates on CXR	Severe AKI He required supplemental oxygen via nasal cannula and RRT	-	AZA withdrawal; TAC dose reduced; PRED dose increased	Inpatient (in medical ward - he remains hemo-dynamical-ly stable)
Alberici F, et al., 2020 [17]	Special report	20 RTR (16male; median age =59 years old; IQR = 51-64); [median = 156 (IQR = 108-240) months post-transplantation]	Fever (20), cough (10) shortness of breath (1), myalgia (1), gastrointestinal symptoms (3), pharyngitis (2),	High levels of CRP, PCT, ferritin, Cr and D-Dimer. Bilateral pulmonary involvement and unilateral changes or no infiltrates on CXR	AKI (-), pneumonia (-), probable sepsis (-). 11 patients required an escalation of the oxygen supplemental therapy (mechanical or non-invasive ventilation). 1 required RRT (hemodialysis) and 4 ICU	Hydroxychloroquine + Lopinavir/ ritonavir(15);Darunavir + ritonavir + Hydroxychloroquine;Tocilizu mab(6); Dexamethasone(11); ephalosporines (7); Beta-lactams (4); Fluoroquinolones (3); Carbapenems (1); Glycopeptides (1)	Fully withdrawal for all patients: (TAC; MMF; Glucocorticoids andmTORi) and started on methylprednisolone.	5 patients died (4 died from complica-tions of the respiratory failure secondary to SARS-Cov2 infection and 1 died of probable bacterial sepsis). 3 patients were discharged and 12 remain hospitalized complications of the respiratory failure secondary to SARS-Cov2 infection and 1 died of probable bacterial sepsis). 3 patients were discharged and 12 remain hospitalized
Meziyerh, S. et al., 2020 [18]	Case report	35-year-old male (52 months post-transplantation)	Fever, cough, malaise, muscle pain, headache, dyspnea with tachypnea, productive cough with sputum without hemoptysis, rhinorrhea, nausea, vomiting, loose stools without abdominal pain	Higher levels of CRP, transaminases, LDH, ESR and Cr, proteinuria, lymphopenia. Bilateral pulmonary involvement on CXR	Renal function deteriorated, respiratory insufficiency (acute respiratory alkalosis with hypoxemia) and rhabdomyolysis. He required supplemental oxygen via nasal cannula. He needed ICU admission and rapid intubation	Chloroquine + Lopinavir/ritonavir; Ceftriaxone/ Loop diuretics	EVE dose reduced at ICU admission and stopped later; inclusion of CsA	Discharged home (follow-up as outpatient)

***Table 1** – Main clinical and laboratory findings of RTR diagnosed with COVID- 19 (cont.)*

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
Kates, O. S. et al., 2020 [19]	Case report	54-year-old male (240 months post-transplantation)	Fever, dry cough, chills, malaise, nausea, vomiting, diarrhoea, dyspnea	Lymphopenia, high levels of Cr, normal white blood cell count and differential. Bilateral patchy consolidations on CXR	Acute-on-chronic kidney injury. He required supplemental oxygen via nasal cannula	Hydroxychloroquine; Chloroquine; Azithromycin; Ceftriaxone	MMF withdrawal; TAC dose reduced; inclusion of PRED	Discharged home
Akalin, E. et al., 2020 [20]	Lettertothe editor	36 RTR (male= 26; mean age = 60 years old)	Fever (21), cough (19), dyspnea (16), myalgia (13), diarrhoea (8)	Low CD3+, CD4+ and CD8+ count, lymphopenia, thrombo-cytopenia, high levels of ferritin, LDH, IL-6 and D-Dimer. Radiographic findings consistent with viral pneumonia	27 patients had consistent diagnosis of viral pneumonia, 11 patients were intubated and received mechanical ventilation, 6 received RRT	Hydroxychloroquine (24); Azithromycin; Leronlimab (6); Apixaban (1); High-dose glucocorticoids; tocilizumab (2).	TAC and MMF/MPA withdrawal	10 patients died; 12 remained hospital-ized; 4 are still intubated; 10 were discharged from Hosp.
The Columbia University Kidney Transplant Program, 2020 [21]	Rapid communi-cation	70-year-old male (60 months post-transplantation)	Fever, cough, fatigue	Lymphopenia, high levels of CRP, LDH and IL-6. No acute findings on CXR	AKI	Hydroxychloroquine; Azithromycin	MPA withdrawal; postponed Belatacept	Dead
		64-year-old male (232 months post-	Fever, cough, fatigue	Bilateral mid and lower lung reticular opacities and hazy bibasilar opacities on CXR	-	Hydroxychloroquin+ Azithromycin	MPA withdrawal	Discharged home
		28-year-old male (42 months post-transplantation)	Fever, cough, myalgia	Lymphopenia, high levels of procalcitonin, ESR and CRP, high white blood cell count. Bilateral haziness and patchy opacities (left greater than right) on CXR	AKI	Hydroxychloroquine; Azithromycin	AZA withdrawal	Discharged home
		51-year-old male (118 months post-transplantation)	Fever, cough	Lymphopenia, high levels of ferritin, ESR, CRP and IL-6, low white blood cell count. Bilateral multifocal patchy opacities on CXR	AKI	Hydroxychloroquine; Azithromycin	MPA withdrawal	Discharged home
		32-year-old female (14 months post-transplantation)	Fever, dyspnea, diarrhoea	High levels of LDH and CRP. Right lower lobe hazy opacity on kCXR	-	Hydroxychloroquine	MMF withdrawal	Discharged home

***Table 1** – Main clinical and laboratory findings of RTR diagnosed with COVID- 19 (cont.)*

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
The Columbia University Kidney Transplant Program, 2020 [21]	Rapid communi-cation	21-year-old male (46 months post-transplantation)	Fever, fatigue, diarrhoea	-	-	-	Unchanged	Discharged home
		36-year-old male (38 months post-transplantation)	Fever, myalgia	Lymphopenia, high levels of ferritin, ESR and CRP, low white blood cell count. Left lower lobe opacities on CXR	-	Hydroxychloroquine	MMF withdrawal	Discharged home
		72-year-old female (49 months post-transplantation	Fever, cough, dyspnea	Lymphopenia, high levels of ferritin, LDH, PCT and CRP, low white blood cell count. Diffuse multifocal on CXR	Intubation with mechanical ventilation required	Hydroxychloroquine	MMF withdrawal	Remains intubated (mechanical ventilation)
		51-year-old female (9 months post-transplantation)	Fever, cough	Lymphopenia, high levels of ferritin, LDH, PCT and CRP, low white blood cell count. Diffuse multifocal on CXR	Intubation with mechanical ventilation required	Hydroxychloroquine	MMF withdrawal	Remains intubated (mechanical ventilation)
		76-year-old male (136 months post-transplantation)	Fever, diarrhoea	Lymphopenia, high levels of ESR, CRP and IL-6. No acute findings on CXR	-	Hydroxychloroquine	Leflunomide withdrawal	Discharged home
		61-year-old male (0 months post-transplantation)	Fever, cough	High levels of ferritin, LDH, procalcitonin, ESR, CRP and IL-6, low white blood cell count. No acute findings on CXR	AKI; Intubation with mechanical ventilation and RRT required	-	TAC and MMF withdrawal; inclusion of PRED	Remains intubated (mechanical ventilation)
		22-year-old male (34 months post-transplantation)	Fever, exertional dyspnea	Lymphopenia, high levels of ferritin, procalcitonin, ESR, CRP and IL-6, low white blood cell count. No acute findings on CXR	Intubation with mechanical ventilation and RRT required	Hydroxychloroquine; Azithromycin; Tocilizumab	TAC and PRED dosereduced	Extubated
		78-year-old male (117 months post-transplantation)	Exertional dyspnea, malaise	Lymphopenia, high levels of ferritin, LDH, ESR, CRP. Bilateral patchy opacities on CXR	AKI; Intubation with mechanical ventilation required	Hydroxychloroquine; Azithromycin	MMF withdrawal	Dead

***Table 1** – Main clinical and laboratory findings of RTR diagnosed with COVID- 19 (cont.)*

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
The Columbia University Kidney Transplant Program, 2020 [21]	Rapid communi-cation	72-year-old female (120 months post-transplantation)	Fever, cough, hemoptysis	High levels of ferritin, LDH, ESR, CRP and IL-6. Diffuse interstitial airspace opacities with upper lobe predominance on CXR	-	Hydroxychloroquine; Azithromycin	MMF withdrawal	Remains hospitalized
		25-year-old female (80 months post-transplantation)	Cough, diarrhoea, emesis	Lymphopenia, high levels of ferritin, ESR and CRP, high white blood cell count. Bilateral hazy opacities on CXR	AKI	Hydroxychloroquine; Azithromycin	MMF withdrawal	Remains hospitalized
Zhu et al., 2020 [22]	**Retrospecti-ve study**	24-year-old male	Fever	High levels of CRP and Cr. Multiple bilateral subpleural patchy consolidation, prominent on the right on Chest CT Scan	Renal damage and significant progressive pneumonia. He required supplemental oxygen via nasal cannula	Unspecified antiviral therapy	Unchanged	Discharged home
		55-year-old male	Cough, short of breath, fatigue	High levels of CRP and Cr, lymphopenia. Multiple bilateral reticular patterns, prominent on the right on Chest CT Scan	Renal damage and significant progressive pneumonia. He required supplemental oxygen via nasal cannula and noninvasive ventilation	IVIG; Unspecified antiviral therapy	MMF/Mi withdrawal; CNI dose reduced	Discharged home
		29-year-old male	Fever, cough, short of breath, fatigue, and diarrhoea	High levels of CRP and Cr, lymphopenia. Multiple patchy ground-glass opacities bilaterally on Chest CT Scan	Renal damage and significant progressive pneumonia. He required supplemental oxygen via nasal cannula	MP iv; Unspecified antiviral therapy	MMF/Mi withdrawal	Discharged home
		30-year-old male	Fever, cough, short of breath, and fatigue	High levels of CRP and Cr, lymphopenia. Multiple bilateral consolidation and ground-glass opacities in the right on Chest CT Scan	Renal damage and significant progressive pneumonia. He required supplemental oxygen via nasal cannula	MP iv; IVIG; Unspecified antiviral therapy	CNI and MMF/Mi withdrawal	Discharged home
		50-year-old male	Fever, cough, short of breath, and fatigue	High levels of CRP and ALT, lymphopenia. Multiple bilateral patchy consolidation on Chest CT Scan	He had significant progressive pneumonia. He required supplemental oxygen via nasal cannula	MP iv; IVIG; Unspecified antiviral therapy	CNI and MMF/Mi withdrawal	Discharged home

Table 1 – *Main clinical and laboratory findings of RTR diagnosed with COVID- 19 (cont.)*

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
Zhu et al., 2020 [22]	**Retrospecti-ve study**	65-year-old female	Fever, cough, short of breath, fatigue, and diarrhoea	High levels of CRP, lymphopenia. Multiple subpleural patchy ground-glass opacities bilaterally on Chest CT Scan	She had significant progressive pneumonia. She required supplemental oxygen via nasal cannula and noninvasive ventilation	MP iv; IVIG; Unspecified antiviral therapy	CNI and MMF/Mi withdrawal	Remains hospitallzed
		52-year-old male	Fever, cough, short of breath, and fatigue	High levels of CRP and ALT, lymphopenia. Bilateral patchy ground-glass opacities on Chest CT Scan	He had significant progressive pneumonia. He required supplemental oxygen via nasal cannula	MP iv; IVIG; Unspecified antiviral therapy	CNI and MMF/Mi withdrawal	Discharged home
		49-year-old male	Fever, cough, short of breath, fatigue, and diarrhoea	High levels of CRP and ALT. Bilateral consolidation and patchy ground-glass opacity in the right side on Chest CT Scan	He had significant progressive pneumonia. He required supplemental oxygen via nasal cannula	MP iv; Unspecified antiviral therapy	CNI and MMF/Mi withdrawal	Discharged home
		59-year-old male	Fever, cough, short of breath, and fatigue	High levels of CRP, ALT and Cr, lymphopenia, decrease in urine volume. Multiple bilateral ground-glass opacities on Chest CT Scan	Renal damage (acute renal allograft failure) and significant progressive pneumonia. He required supplemental oxygen via nasal cannula and noninvasive ventilation	MP iv; IVIG; Unspecified antiviral therapy	CNI and MMF/Mi withdrawal	Dead
		37-year-old female	Fever, cough, short of breath, and fatigue	High levels of CRP, ALT and Cr, lymphopenia. Multiple bilateral patchy consolidation and ground-glass opacities on Chest CT Scan	Renal damage and significant progressive pneumonia. She required supplemental oxygen via nasal cannula	MP iv; IVIG; Unspecified antiviral therapy	CNI andMMF/Mi withdrawal	Discharged home
Arpali et al., 2020 [23]	Case Report and Review of the Literature	28-year-old female (6 months post-transplantation)	Fever, malaise, sore throat and rhinorrhea	Normal markers of renal function and platelets accounts, lymphopenia, elevated CRP, high NLR. Mild hyperemia of the tonsils, pharyngeal mucosa. No pathological findings on CXR and on CT scan of her chest	No complications	Oseltamivir; Amoxicillin	Unchanged	Discharged home

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
Bussalino et al., 2020 [24]	Case Report	32-year-old male (30 months post-transplantation)	Fever, dyspnea, nonproductive-cough	Lymphopenia; Low CD4+, CD8+, CD3+ count; monocytosis, thrombocy-topenia, reduction of PT. CRP elevation, slightly Lymphopenia; Low CD4+, CD8+, CD3+ count; monocytosis, thrombocy-topenia, reduction of PT. CRP elevation, slightly elevated levels of PCT. High levels of Cr and decreased levels of eGFR and proteinuria; Increased levels of ferritin, transami-nases, IL-6 and LDH. Diffuse septal thickening in the absence of areas of consolidation on CXR	Pneumonia, renal function impairment, probable respiratory alkalosis. Oxygen-administration via nasal cannula.	Hydroxy-chloroquine; Oseltamivir; Ceftaroline; PRED (increased dose)	Unchanged	Discharged home
Zhong Z et al., 2020 [25]	Case Report	48-year-old male (204 months post-transplantation)	Persistent fever, cough, sputum, muscle aches, fatigue, chest tightness	Low red blood cell account, low level of haemoglobin, leukopenia thrombo-cytopenia, lymphopenia, high levels of Cr and CRP. Bilateral scattered flocculent fuzzy lesions on pulmonary CT	Pneumonia, severe bone marrow suppression, anaemia Acuteallograft-rejection	Oseltamivir; Abidol; Moxifloxacin; Recombinant human interferon alpha; MP; IVIG; Blood transfusion	TAC dose reduced and MMF withdrawal	Discharged home
Marx et al., 2020 [26]	Lettertothe Editor	58-year-old male (38 months post-transplantation)	Fever, milddyspnea, cough	lymphopenia,Slight increase in IL-6 levels and CRP, Limited peripheral pulmonary ground-glass opacities on chest CT	Mild clinical course of pneumonia	-	Belatacept and MMFwithdrawal; CsA initialed; PRED uncharged	Discharged home
Ning, L. et al. 2020 [27]	Case Report	29-year-old male (15 months post-transplantation)	Fever, persistent fatigue and chills, mild chest tightness, nasal stuffiness, loss of appetite, nausea, vomiting, dizziness	Leukocytosis, mild thrombocy-topenia, hematuria, hyponatremia, hypoalbuminemia, elevated Cr level, oliguria. Bilateral diffuse ground-glass opacity on chest CT	Atypical pneumonia, no serious hepatic and renal dysfunction	Lopinavir/ritonavir; Gamma-globulin; Probiotics; Trimethoprim + sulfamethoxazole; Moxifloxacin; Fluid administration based on urine volume	Unchanged	Discharged home

Table 1 – *Main clinical and laboratory findings of RTR diagnosed with COVID- 19 (cont.)*

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
Zhang, H. et al., 2020 [28]	Case Report	38-year-old male (04 months post-transplantation)	Fever, cough	Lymphopenia, reduced of haemoglobin levels, proteinuria, increased levels of CRP, CR, transaminases, LDH, Chest CT showed deterioration	pneumonia	Oseltamivir; MP;	TAC and MMF withdrawal	Discharged home
		38-year-old male (04 months post-transplantation)	Fever, cough	Lymphopenia, reduced of haemoglobin levels, proteinuria, increased levels of CRP, CR, transaminases, LDH, Chest CT showed deterioration	pneumonia	Oseltamivir; MP;	TAC and MMF withdrawal	Discharged home
		64-year-old male (50 months post-transplantation)	Fever, cough, dyspnea, sputum, chest tightness	Leukocytosis, neutronphilia, lymphopenia, proteinuria, anuria. increased levels of ESR, D-Dimer, CRP, CR, LDH; hyponatremia, Chest CT showed deterioration	Pneumonia, with ventilatory therapy and AKI	Oseltamivir; MP; IVIG,	TAC and MMF withdrawal	Remained-hospitalized
		37-year-old female (08 months post-transplantation)	Fever, cough	Lymphopenia, decreased levels of haemoglobin, increased levels of ESR, D-Dimer, CRP, CR, LDH, transaminases, hyponatremia, proteinuria. Chest CT showed-deterioration	Pneumonia	Oseltamivir; MP; cefixime, IVIG,	TAC reduced and MMF withdrawal	Remained-hospitalized
		47-year-old male (13 months post-transplantation)	Fever, cough, sputum, chest tightness	Lymphopenia, decreased levels of haemoglobin, increased levels of ESR, CRP, CR, LDH, hyponatremia, proteinuria. Chest CT showed-deterioration	Pneumonia	Oseltamivir, MP	TAC and MMF withdrawal	Remained-hospitalized
		38-year-old male (33 months post-transplantation)	Fever, cough, sputum, chest tightness	Lymphopenia, increased levels of ESR, CRP, hyponatremia. Chest CT showed-deterioration	Pneumonia	Oseltamivir; MP;	Unchanged	Discharged home

Table 1 – *Main clinical and laboratory findings of RTR diagnosed with COVID- 19 (cont.)*

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
Huang J. et al., 2020 [29]	Case Report	58-year-old male (145 months post-transplant-ation)	Fever, dry cough, shortness of breath	Lymphopenia, low CD4+ and CD8+ count. CT scan revealed typical signs of COVID-19 pneumonia.	Pneumonia. He needed mecha-nical ventilation and developed multiorgan failure (lung, kidney and heart)	Oseltamivir; Moxifloxacin; MP; High flow humidification oxygen inhalation therapy	Unchanged	Dead
Chen S. et al., 2020 [30]	Case Report	50-year-old male (48 months post-transplanttion)	Fever, cough	Lymphopenia, leukopenia, high levels of IL-6 and LDH. Minimal interstitial lesions on CXR	Mildclinicalcourse	Lopinavir/ritonavir, Ceftriaxone	Unchanged	Discharged home
Gandolfini et al. 2020 [32]	Lettertothe editor	75-year-old male (120 months post-transplan-tation)	Fever, cough, myalgia, dyspnea	High levels of IL-6, CRP Cr, LDH and Typical radiological findings of COVID-19 pneumonia with extensive bilateral ground-glass opacities on lung CT scan	Pneumonia, transient liver failure. non-invasive ventilation	Hydroxychloroquine Lopinavir/ ritonavir	TAC and MMF withdrawal PRED unchanged	Dead
		52-year-old female (08 mon-ths post-trans-plantation)	Fever, cough, myalgia, dyspnea, diarrhoea.	High levels of IL-6, CRP Cr, LDH and D-dimer. Typical radiological findings of COVID-19 pneumonia with extensive bilateral ground-glass opacities on lung CT scan	Pneumonia, AKI, transient liver failure. non-invasive ventilation	Hydroxychloroquine, Darunavir / cobicistat	TAC and MMF withdra-wal, PRED unchanged	Discharged home
Guillen et al. 2020 [33]	Case Report	50-year-old male (48 months post-transplan-tation)	Fever, malaise, vomiting, mild dehydration, productive cough, conjunctivitis and high blood pressure	Lymphopenia, leukocytosis, thrombocytopenia, low levels of haemoglobin. High levels of D-Dimer, PCT and CRP, slight elevation of Cr levels and reduction of eGFR, hyponatremia. Medium lobe consolidation on the posteroanterior chest that progressed to diffuse bilateral infiltrates on CXR	Mild kidney function impair-ment, pneumonia. He was intubated with ventilatory supportive care	Acetaminophen; Ceftriaxone; Azithromycin; Lopinavir + Ritonavir; Interferon Beta Hydroxychloroquine; Ceftaroline; Meropenem	TAC and EVE withdrawal	Patient remained hemo-dynamically stable on respiratory supportive therapy in the ICU

Table 1 – *Main clinical and laboratory findings of RTR diagnosed with COVID- 19 (cont.)*

Article	Type of publication	Patients	Main symptoms	Main laboratory and imaging results	Complications	Anti-COVID-19 Therapy/ Other treatments	Management of immunosuppressive therapy	Outcomes
Zhu L et al. 2020 [34]	Case Report	52-year-old male (144 months post-transplantation)	Fever, fatigue, dyspnea, tightness and pain in the chest, nausea, loss of appetite, intermittent abdominal pain, occasional dry coughs, headache	Lymphopenia, neutrophilia, monocytosis, increased of ESR, CRP, ALT, IL-2 r eceptor, IL-6 and TNF levels, proteinuria. Multiple patchy ground-glass density shadows in the upper lobe of both lungs and the lower lobe of the left lung and a small patchy ground-glass density shadow in the middle lobe of the right lung on CT scan	Pneumonia. He needed oxygen via nasal catheter and lost 10 kg of body weight (poor eating)	Umifenovir; Moxifloxacin; MP; IVIG; Biapenem; Interferon α; Glycyrrhizic Acid Diamine	Fully withdrawal:TAC; MMF and PRED	Discharged home

Table 1 - Legend

AKI: acute kidney injury, ALT: alanine aminotransferase, ARDS: acute respiratory distress syndrome, AST: aspartate aminotransferase, AZA: azathioprine, BUN: blood urea nitrogen, CNI: calcineurin, CPAP: continuous positive airway pressure therapy, Cr: creatinine, CRP: C-reactive protein, CsA: Cyclosporine, CT: computed tomography, CVVH: continuous venovenous hemodiafiltration, CXR: chest X-ray, eGFR: estimated glomerular filtration rate, ESR: erythrocyte sedimentation rate, EVE: everolimus, ICU: intensive care unit, IL-6: interleukin 6, IL-2: interleukin 2, IQR: interquartile range, IV: intravenous, IVIG: Intravenous immunoglobulin, LDH: lactic dehydrogenase (LDH), Mi: mizoribine, MMF: Mycophenolate mofetil, MP: methylprednisolone, MPA: mycophenolate acid, mTORi: mammalian target of rapamycin inhibitors, NLR: neutrophil-lymphocyte ratio, NT-proBNP; N-terminal prohormone of brain natriuretic peptide, PCT: procalcitonin, PRED: prednisone, PT: prothrombin Time, RRT: renal replacement therapy, RTR: renal transplant recipients, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, TAC: tacrolimus, TNF: tumor necrosis factor, (-): data not available.

RESUMO

COVID-19 é uma doença emergente associada principalmente à Síndrome Respiratória Aguda Grave (SARS). Essa doença causa a liberação de uma tempestade de citocinas em resposta à infecção viral e pode levar a várias complicações sistêmicas. A lesão renal aguda (LRA) é uma dessas complicações e a terapia renal substitutiva pode ser necessária para o paciente infectado. Nesse contexto, receptores de transplante renal (RTR) e pacientes com doença renal crônica são grupos de risco para COVID-19, devido ao aumento do estado inflamatório e da disfunção endotelial. Além disso, a terapia imunossupressora de manutenção em RTR também pode ser outro fator complicador, uma vez que influencia a resposta do sistema imunológico contra patógenos, incluindo SARS-CoV-2. Porém, acredita-se que os piores desfechos da COVID-19 se devam mais a uma resposta inflamatória exagerada do que à ação direta do vírus. Portanto, em um estado hiper inflamatório, a terapia de imunossupressão poderia ser benéfica. Esta revisão narrativa tem como objetivo apresentar os principais achados clínicos e laboratoriais de 22 estudos envolvendo RTR afetados pela COVID-19, podendo contribuir para o gerenciamento da COVID-19 e suas consequências nesse grupo de risco.

Descritores: Doenças Transmissíveis; Infecções por Coronavirus; Insuficiência renal; Transplante renal.

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Role of authors

SRM and LVA contributed to the review of all articles,
writing of the manuscript and interpretation of the results.
APLM was involved in the planning and supervision of the work.
JKPR, BEFM, KPF, KBG, and LMSD made substantial contributions and critical reviews.
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All authors discussed the results and commented on the manuscript.