REVIEW

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Kidney transplant recipients infected by COVID-19: Review of the initial published experience

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Abstract

There is an accumulating body of literature surrounding the impact of COVID-19 infection in solid organ transplant recipients. The aim of this review was to summarize the existing literature specifically in kidney transplant (KTx) recipients, with an emphasis on the epidemiology, clinical presentation, laboratory findings, post-operative outcomes, and therapeutic strategies currently employed. We identified thirty-seven studies published between January 1, 2020, and June 10, 2020, that were included in our analysis. As is reported in the general population, there is a wide variation in COVID-19 presentation among KTx patients, ranging from asymptomatic to life-threatening end-organ failure. The most common symptoms are predominantly respiratory and associated with fever. On laboratory evaluation, many patients present with lymphopenia and increased CRP, which are both associated with inferior outcomes. The majority of patients with severe symptoms have been managed with reduction of immunosuppression, including decreased doses of CNIs and withdrawal of MMF. Lastly, although there are no high-level data supporting the use of immunomodulatory drugs, such as IL-6 inhibitors, early experiences have suggested these drugs may improve outcomes in KTx patients with severe COVID-19.

KEYWORDS
coronavirus, COVID-19, kidney transplantation, SARS-CoV-2

1 | INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic.[1] The Centers for Disease Control and Prevention have identified immunocompromised patients, including those requiring immunosuppression following transplantation, as high risk to develop severe COVID-19.[2] Although it is well described in transplantation that treatment of viral infections includes a reduction in immunosuppression, there are no established guidelines specifically recommending an optimal approach in the management of immunosuppression in SARS-CoV-2-infected patients.[3] Furthermore, early clinical studies have suggested that some agents with immunosuppressive properties such as dexamethasone and

tocilizumab[4,5] have salutary effects, questioning the a priori assumption that immunosuppressive reduction is prudent.

Since the onset of the COVID-19 pandemic, a growing body of literature has described the incidence, clinical course, and outcomes of COVID-19 in solid organ transplant recipients.[6] Understandably however, the majority of published studies represent small, single-center experiences and therefore do not provide a comprehensive overview of COVID-19 risk in these patients. Intuitively, one would expect kidney transplant (KTx) recipients are at higher risk of progression from subclinical SARS-CoV-2 infection to symptomatic COVID-19 when compared to immunocompetent individuals; however, the true rates of progression are unknown, and early CDC reports suggest that asymptomatic infection is common.[7] In addition, given transplant patients are often engaged in frequent clinical

follow-up, determining the true incidence of disease progression would be confounded by ascertainment bias. Regardless, it is reasonable to expect that the clinical response to COVID-19 may differ in transplant patients and specifically among kidney recipients,[8,9] given the specific comorbidities unique to this patient population such as hypertension, which itself has been identified as a risk factor for COVID-19 mortality.[10]

The aim of this review was to summarize the current literature describing the natural history of COVID-19 in KTx recipients, with an emphasis on epidemiology, presentation, laboratory findings, outcomes, and potential therapeutic strategies.
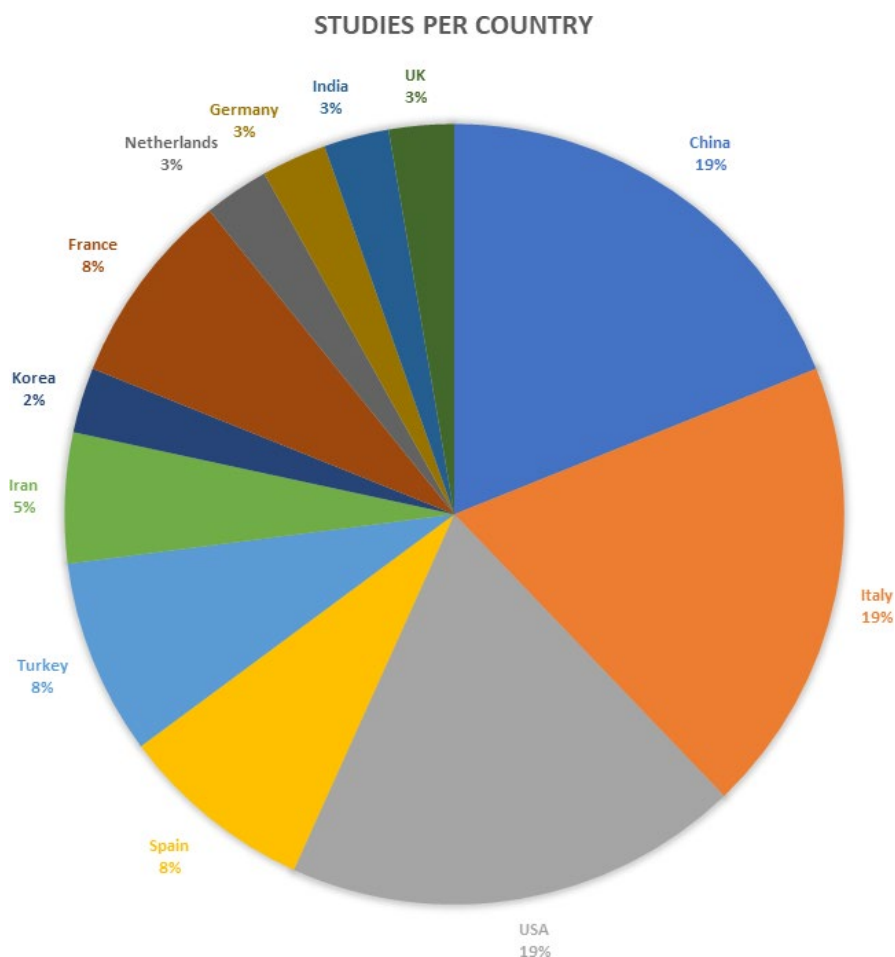
2 | METHODS

We queried the PubMed database for articles published between January 1, 2020, and June 10, 2020, using the key words ''coronavirus'', ''COVID-19'', ''kidney transplantation'' and ''SARS-CoV-2''. We identified 46 abstracts eligible for further analysis. We excluded studies due to lack of data granularity on the KTx recipients[8,9,11-14] and reports of pediatric,[15] dual or multiorgan transplantation.[16,17] In total, 37 studies were included in the final analysis.[18-54] All studies were evaluated to prevent overlap of published patients and related data.

3 | RESULTS

Twelve of 37 (32.4%) articles were case series while the remaining 25 (67.6%) were individual case reports. Not surprisingly, most publications came from China, USA, and Italy, countries with high incidence of COVID-19 (Figure 1).[55]

3.1 | Epidemiology

We identified 221 KTx recipients infected by COVID-19.[18-54] Among these, 156 (70.6%) were men and 65 (29.4%) women. The average age at the time of diagnosis was 50.8 years (SD = 10.8, range = 28-78); however, the average age of patients with severe symptoms was significantly higher (58.3 ± 8.4, $P = .005$), which is comparable to the non-transplant COVID-19 literature.[56] Most patients in our cohort had multiple comorbidities with the most prevalent being hypertension, diabetes, cardiovascular disease, chronic kidney disease, and obesity, all of which are disproportionately represented in the KTx patient population. Less than 10% of the patients had a history of malignancy (solid organ or hematologic), perhaps reflecting those precluded from transplant eligibility due to active malignancy. Reporting of donor-specific information was available in all studies, but most kidney allografts came from deceased donors (>80%).

STUDIES PER COUNTRY

UK 3%
India 3%
Germany 3%
Netherlands 3%
France 8%
Korea 2%
Iran 5%
Turkey 8%
Spain 8%
USA 19%
Italy 19%
China 19%

FIGURE 1 Distribution of published articles per country

These trends are comparable to the demographics of the general KTx populations.[57] Many studies (31/37) reported the time from KTx to COVID-19 diagnosis[18,21-28,30-40,42-53]; 77.4% of KTx recipients received their allograft more than 1 year before COVID-19 diagnosis (range 8 days-31 years). It is unclear whether this trend is simply a reflection of the patients with KTx or it disproportionally represents chronic transplant patients.

3.2 | Symptomatology and laboratory findings

Most COVID-19-positive KTx recipients included in the analyzed literature were treated as inpatients (193/221, 87.3%). All included studies reported symptoms at the time of initial physical exam.[18-54] Fever was the most common symptom (84.5%), followed by cough (64%), and hypoxia mandating oxygen supplementation (54%). Other reported, but less common symptoms included gastrointestinal (diarrhea, abdominal pain) and musculoskeletal pain (arthralgias and myalgias).

Laboratory evaluation was included in 33 of 37 studies.[18,19,21-34,36-44,46,48-54] Most patients presented with lymphopenia and lymphopenia-associated immunosuppression (84.4%) either at the time of admission or during their hospitalization. Most transplant patients have some degree of chronic lymphopenia, and indeed, 70% of KTx receive lymphocyte depletional induction; thus, it is not clear whether this is a viral effect or a general characteristic of the KTx population.

There are two proposed mechanisms that might lead to lymphopenia during COVID-19 infection; (a) the virus may directly infect lymphocytes or lymphatic organs resulting in lymphocyte dysfunction or death, or (b) upregulation of inflammatory cytokines such as tumor necrosis factor-α, IL-6, and others might directly induce lymphocyte apoptosis.[58] A recent meta-analysis showed that lymphopenia at admission was correlated with worse outcomes in patients with COVID-19, including increased mortality and intensive care unit (ICU) admission.[59] In our analysis, very few patients were found to have leukopenia or leukocytosis, mostly attributable to septic complications during their admission.

Another commonly utilized laboratory marker is C-reactive protein, which was elevated in 78.8% of the patients. Other inflammatory markers such as interleukin-6 (IL-6), ferritin, and procalcitonin are less consistently reported but have been found elevated in many patients. Finally, 58.5% of the patients presented or developed acute kidney injury (AKI) during their admission. Most of these patients recovered without intervention although four patients required renal replacement therapy and only one developed chronic kidney disease during follow-up. Of interest, 12 patients developed moderate hyponatremia (121-131 mEq/L), that was resolved during the index admission. One proposed mechanism of hyponatremia in COVID-19-infected patients hypothesizes that increased inflammation leads to hypersecretion of antidiuretic hormone. Still, this phenomenon appears to be self-limited and its clinical implications are not well described in the literature.[60]

TABLE 1 Demographic data of the study

Variable	Value	References
Mean age (years)	50.8 ± 10.8	[18-54]
<60 years	183 (83%)	
Gender		
Male (%)	156 (70.5)	[18-54]
Female (%)	65 (29.5)	
Symptoms		
Fever (%)	159/188 (84.5)	[18-44,46-54]
Cough (%)	101/152 (66.4)	
Hypoxia (SpO$_2$ <92%) (%)	89/165 (54)	
Systems involved		
Respiratory	221/221 (100)	[18-54]
Gastrointestinal	69/221 (31.2)	
Musculoskeletal	35/221 (15.8)	
Other	11/221 (5)	
Laboratory results		
Lymphopenia	130/156 (84.4)	[18,19,21-34,36-44,46,48-54]
Leukocytosis	15/156 (10)	
Leukopenia	3/156 (2)	
Thrombocytopenia	24/156 (15.4)	
Transaminitis	40/126 (31.7)	
Hyponatremia	12/156 (7.7)	
Elevated C-Reactive Protein (CRP)	93/118 (78.8)	
Elevated creatinine from baseline	48/82 (58.5)	
Radiographic presentation		
Bilateral opacities	124/158 (78.5)	[18,19,21-28,30-34,36-42,44,46-54]
Lower lobe involvement	21/30 (70)	
Normal	15/158 (9.5)	
Time since transplant		
<1 y (%)	40/179 (22.6)	[18,21-28,30-40,42-53]
More than 1 y (%)	139/179 (77.4)	
Treatment setting		
Inpatient	193/221 (87.3%)	[18-54]
Outpatient	128/221 (12.7%)	

Regarding radiographic findings in KTx COVID-19-infected patients, 78.5% presented with bilateral ground-glass opacities in both chest plain radiograph and CT scan of the chest.[18,19,21-28,30-34,36-42,44,46-54] Of note however, about 10% had normal imaging at the time of presentation. Less common findings included unilateral opacities and septal interstitial changes. Lower lung fields were usually affected (70%). Some discrepancies between Xray and CT scan findings were noted in few patients (negative Xraypositive CT scan).

Table 1 summarizes the demographic, clinical, and laboratory data of our cohort.

TABLE 2 Summary of the treatment modalities, outcomes, and management of immunosuppression of KTx recipients with COVID-19

Author	Management of immunosuppression	Admission to intensive care unit	Other treatment	Mortality
Abrishami et al[18]	• Switch to intravenous steroids • Decreasing dose of MMF • Decreasing dose of tacrolimus • Decreasing dose of sirolimus	10/12	• Hydroxychloroquine • Lopinavir/ritonavir • Broad spectrum antibiotics • Intravenous immunoglobulin	8/12
Cheng et al[26]	• Withdrawal of MMF and tacrolimus • Continue steroids	NR	• Arbibol • Moxifloxacin • Intravenous immunoglobulin	0/2
Fontana et al[30]	• Decreasing 50% the dose of CyA	NR	• Tocilizumab • Hydroxychloroquine • Broad spectrum antibiotics	0/1
Banerjee et al[23]	• Withdrawal of MMF • Withdrawal of decreasing Tac • Withdrawal of AZA • Continue Steroids	2/7	• Oseltamivir • Broad spectrum antibiotics	1/7
Alberici et al[21]	• Withdrawal of MMF • Withdrawal of Tacrolimus • Withdrawal of CyA • Withdrawal of sirolimus • Continue steroids	4/20	• Lopinavir/ritonavir • Darunavir + ritonavir • Hydroxychloroquine • Tocilizumab • Broad spectrum antibiotics	5/20
Gautier-Vargas et al[33]	• Withdrawal of MMF • Decreasing dose of CyA	NR	• Broad spectrum antibiotics	0/1
Kemmner et al[37]	• Withdrawal of MMF • Switch to CyA/steroids	0/1	• Broad spectrum antibiotics • Hydroxychloroquine	0/1
Akalin et al[19]	• Withdrawal of MMF • Withdrawal of tacrolimus • Continue steroids	NR	• Broad spectrum antibiotics • Hydroxychloroquine • Leronlimab • Tocilizumab	10/36
Akdur et al[20]	• Withdrawal of MMF • Withdrawal of CNIs • Withdrawal of steroids	NR	• Hydroxychloroquine	0/1
Shingare et al[51]	• Withdrawal of MMF • Steroid tapering • Decreasing of tacrolimus	0/2	• Broad spectrum antibiotics • Hydroxychloroquine	0/2
Kocak et al[39]	• Withdrawal of Tacrolimus • Withdrawal of MMF • Continue steroids	0/2	• Oseltamivir • Hydroxychloroquine	0/2
Hussain et al[35]	• Reduction of immunosuppression in hospitalized patients only, not specified	0/22	• NR	0/22
Faguer et al[29]	• Withdrawal of MMF • Withdrawal of Tacrolimus	1/1	• Broad spectrum antibiotics • Tocilizumab	0/1
Marx et al[42]	• Withdrawal of MMF • Withdrawal of belatacept • Start CyA • Continue steroids	0/1	• Broad spectrum antibiotics	0/1
Wang et al[52]	• Unchanged	0/1	• Lopinavir plus ritonavir • Ribavirin • Interferon α-2b • Methylprednisolone	0/1
Zhang et al[53]	• Withdrawal of MMF • Continue steroids • Withdrawal or decrease of Tacrolimus	0/5	• Oseltamivir or arbidol • Broad spectrum antibiotics • Intravenous immunoglobulin	0/5

(Continues)

TABLE 2 (Continued)

Author	Management of immunosuppression	Admission to intensive care unit	Other treatment	Mortality
Zhu et al[54]	• Withdrawal of all immunosuppression	0/1	• Umifenovir • Broad spectrum antibiotics • Intravenous immunoglobulin • Interferon α	0/1
Guillen et al[34]	• Withdrawal of everolimus • Withdrawal of tacrolimus • Continue steroids	1/1	• Broad spectrum antibiotics • Lopinavir/Ritonavir • Hydroxychloroquine • Interferon Beta	0/1
Seminari et al[50]	• Unchanged	0/1	• Broad spectrum antibiotics	0/1
Arpali et al[22]	• Unchanged	0/1	• Broad spectrum antibiotics • Oseltamivir	0/1
Gandolfini et al[32]	• Withdrawal of Tacrolimus • Withdrawal of MMF • Continue steroids	2/2	• Hydroxychloroquine • Lopinavir + ritonavir • Darunavir + cobicistat • Colchicine	1/2
Chen et al[25]	• Withdrawal of MMF • Decrease 50% in Tacrolimus	1/1	• Umifenovir • Intravenous immunoglobulin • Broad spectrum antibiotics	0/1
Mella et al[43]	• Withdrawal of tacrolimus • Withdrawal of MMF • Continue steroids	3/6	• Broad spectrum antibiotics • Intravenous immunoglobulin • Tocilizumab • Hydroxychloroquine • Darunavir/Ritonavir	3/6
Ning et al[49]	• Unchanged	0/1	• Lopinavir/ritonavir • Broad spectrum antibiotics	0/1
Bussalino et al[24]	• Unchanged	0/1	• Hydroxychloroquine • Oseltamivir • Broad spectrum antibiotics	0/1
Kates et al[36]	• Withdrawal of MMF • Decreasing dose of tacrolimus • Continue steroids	0/1	• Broad spectrum antibiotics • Hydroxychloroquine	0/1
Meziyerh et al[44]	• Withdrawal of everolimus • Switch to CyA • Continue steroids	1/1	• Broad spectrum antibiotics • Hydroxychloroquine • Lopinavir/ritonavir	0/1
Kim et al[38]	• Withdrawal of tacrolimus • Withdrawal of MMF • Continue steroids	0/2	• Broad spectrum antibiotic • Hydroxychloroquine • Lopinavir/ritonavir	0/2
Nair et al[47]	• Withdrawal of MMF • Withdrawal of tacrolimus • Withdrawal of sirolimus	5/10	• Broad spectrum antibiotics • Hydroxychloroquine	3/10
Namazee et al[48]	• Reduced MMF • Reduced CyA	1/1	• Hydroxychloroquine • Lopinavir/Ritonavir • Oseltamivir • Broad spectrum antibiotics	1/1
Montagud-Marrahi et al[45]	• Withdrawal of MMF and/or mTOR inhibitors in all patients • Withdrawal of CNI if lopinavir/ritonavir is prescribed due to interactions • Continue steroids	13/33	• Broad antibiotics • Lopinavir/ritonavir • Hydroxychloroquine • Tocilizumab • Interferon beta • Steroid pulses • Anakinra	2/33
Zhang M et al[41]	• Discontinuation of Tacrolimus and MMF • Continue steroids	0/1	• Umifenovir • Broad spectrum antibiotics	0/1

(Continues)

TABLE 2 (Continued)

Author	Management of immunosuppression	Admission to intensive care unit	Other treatment	Mortality
Lauterio et al[40]	• Stop CyA • Stop Everolimus • Continue steroids	1/1	• Lopinavir/ritonavir • Hydroxychloroquine • Broad spectrum antibiotics • Tocilizumab	0/1
Crespo et al[28]	• Withdrawal of MMF • Withdrawal of CNI	2/2	• Broad spectrum antibiotics • Steroids • Hydroxychloroquine • Lopinavir/ritonavir • Tocilizumab	8/16
Fung et al[31]	• Withdrawal of MMF • Decreased Tacrolimus • Continue Steroids	2/7	• Broad spectrum antibiotics • Convalescent plasma • Hydroxychloroquine • Tocilizumab	0/7
Columbia University Kidney Program[27]	• Withdrawal of MMF • Withdrawal of belatacept	4/15	• Tocilizumab • Hydroxychloroquine • Broad spectrum antibiotics	2/15
Morillas et al[46]	• Withdrawal of MMF • Decreased tacrolimus • Continue steroids	2/2	• Tocilizumab • Hydroxychloroquine • Lopinavir/ritonavir • Broad spectrum antibiotics	0/2

Abbreviations: CNI, calcineurin inhibitors; CyA, cyclosporine; MMF, Mycophenolate Mofetil; mTOR, mammalian target of rapamycin; NR, not reported.

3.3 | Outcomes

Regarding ICU admission rates, 33.7% (55/163) of KTx recipients needed ICU care.[18,21-25,27-29,31,32,34-54] More than 80% of them were older than 60 years of age. This is nearly double that reported in the liver transplant population reported in the ELITA/ELTR COVID-19 registry (15%).[61] Pooled data in cancer patients reported an even lower ICU admission rate of 12.6%.[62] These findings might indicate a need for increased resource in the kidney transplant setting and may influence the decision to perform this semi-elective operation considering ICU availability during pandemic.

Cumulative COVID-related mortality was 19.9% (44/221)[18-54]; 65.9% (29/44) of these deaths were noted in KTx recipients older than 60 years of age. Also, 68.1% (30/44) of the deaths occurred in KTx recipients with longer time since transplantation (>1 year). These findings are of paramount clinical importance since due to intensive immunosuppression, recent transplant recipients (<3 months post-transplant) were expected to develop severe disease due to COVID-19 more frequently than old transplants. It is unclear whether this trend is simply a reflection of the patients with KTx or it disproportionally represents chronic transplant patients. Data from the ELITA/ELTR COVID-19 registry showed similar findings in liver transplant patients. More specifically, the mortality in liver transplant recipients was 16% and was higher in older recipients (>60 years old) and in patients with longer time since transplantation (>2 years).[61] Data from cancer literature also report variable mortality rates related to COVID-19, though a recent meta-analysis estimates a 16.6% mortality among cancer patients with concomitant COVID-19.[62]

3.4 | Treatment and management of immunosuppression

Currently, there are no FDA-approved therapeutic drugs or vaccines for SARS-CoV-2. Most of the treatment strategies have been adopted from previous experience treating SARS-CoV and MERS-CoV and emphasize supportive symptom management. Although treatment of COVID-19 among KTx recipients varied significantly among studies,[18-34,36-54] 97.2% of patients received broad spectrum antibiotics empirically.

There is no consensus on the management of immunosuppression among KTx recipients with COVID-19, and the present literature review found a significant heterogeneity in management strategies among studies and patients.[18-54] More than 80% of the patients included in our analysis were on standard triple therapy with MMF, calcineurin inhibitors and steroids. Most patients were on tacrolimus, though cases of patients on mTOR inhibitors, azathioprine and belatacept are also reported. In general, the mainstay of treatment was the decrease or withdrawal of immunosuppression. Only five studies reported no change in immunosuppression.[22,24,49,50,52] In the studies where management of antimetabolite therapy was reported, most patients had MMF withheld and very few continued MMF with decreased dose. A smaller proportion of KTx had the calcineurin inhibitor held or decreased. Some studies reported switching of tacrolimus to cyclosporine. In patients on costimulation blockade, data are limited however patients had belatacept withheld, noting that the half-life of infusional therapies makes complete abrupt withdrawal impossible.[27,42] Interestingly, the two reports of

patients on belatacept had relatively mild COVID-19 courses that was partially attributed to the belatacept-related blockade of cytokine production.[42] Finally, all patients on mTOR inhibitors had their therapy withdrawn or decreased. Very few studies reported data on induction therapy at the time of transplant. Most KTx COVID-19-infected patients had received induction with ATG or basiliximab. The majority of patients remained on steroids. Besides the effect of steroids in preventing acute rejection, a recent trial showed that dexamethasone can be beneficial in terms of reduction of mortality risk in patients with severe COVID-19, including mechanically ventilated patients.[63] None of the studies reported any documented episode of acute rejection due to changes in immunosuppression.

Hydroxychloroquine sulfate and chloroquine phosphate, historically, anti-malaria drugs, have also been investigated for treatment of COVID-19 in clinical trials.[64,65] In the current study, hydroxychloroquine was used in 54.8% (121/221) of KTx patients, most frequently in those with severe symptomatology[18-21,24,27,28,30-32,34,36-41,43-48,51] and in combination with antibiotics and immunomodulatory drugs. Several case reports noted improvement or even resolution of symptoms, although it is important to acknowledge potential toxicities associated with hydroxychloroquine, as well drug interaction effects with cyclosporine, tacrolimus, and mammalian target of rapamycin inhibitors (mTORs). Hydroxychloroquine and lopinavir/ritonavir may interact causing a prolongation of the cardiac QTc interval; however, currently this complication is unreported specifically in KTx patients. Like tacrolimus, hydroxychloroquine is also a substrate of CYP3A, necessitating careful monitoring of drug levels if concurrently used. A recent report by Xia et al[66] have recommended against using immunosuppressants in combination with protease inhibitors or hydroxychloroquine due to over-immunosuppression and potential cardiac toxicity.

Other experimental treatments have included antiviral drugs such as protease inhibitors (lopinavir), ritonavir, darunavir (protease inhibitors), oseltamivir (neuraminidase inhibitor), ribavirin (nucleoside inhibitor), and umifenovir, alone or in combination.[18-34,36-54] Early data on hospitalized patients with severe COVID-19 showed potential clinical benefit,[67] although multiple randomized clinical trials are ongoing. In the KTx setting, some patients with severe symptoms seem to benefit from combined therapies, including antiviral drugs, but the contribution of individual treatment to clinical outcome cannot be evaluated or justified. Furthermore, it is important to acknowledge that protease inhibitors are known inhibitors of cytochrome P450 3A (CYP3A), of which tacrolimus is a substrate; therefore, careful monitoring of tacrolimus levels is critical in patients during and after treatment with this class of drugs.[68]

Immunomodulatory drugs may hold promise for the management of cytokine release syndrome in COVID-19 including tocilizumab, an inhibitor of the pro-inflammatory cytokine IL-6.[69] Among the case reports included in this analysis, tocilizumab was used in few patients in combination with antibiotics and antiviral drugs. Patients were considered for tocilizumab only after withdrawal of MMF and CNIs. Most patients showed improvement or even recovered after tocilizumab administration.[19,21,27-31,40,43,45,46] In the same setting, intravenous immunoglobulins (IVIG) have

been proposed for the use in patients with severe COVID-19 to counteract inflammation and endothelial activation.[70] In KTx population, its use was limited. Finally, one case series reported the use of convalescent plasma therapy in KTx patients with COVID-19.[31] Currently, there are no data on the role of convalescent plasma and hyperimmune immunoglobulins in the management of COVID-19 in solid organ recipients but reports from non-transplant COVID-19 literature are conflicting.[71]

Table 2 summarizes the treatment modalities, outcomes, and management of immunosuppression of KTx recipients with COVID-19.

4 | CONCLUSIONS

This review highlights the clinical spectrum currently reported in COVID-19-infected KTx patients, which may vary from asymptomatic and treated on an outpatient basis, to severely symptomatic mandating ICU admission. The symptoms are predominantly respiratory and associated with fever. On laboratory evaluation, most patients present with lymphopenia and increased CRP, both of which are associated with inferior outcomes. CT scan of the chest is the most sensitive imaging modality for diagnosis, with the most common finding being bilateral ground-glass opacities. Most patients with severe symptoms are treated with reduction of immunosuppression, including decreasing doses of CNIs and withdrawal of MMF along with supportive therapy. Currently, there is no high-level evidence supporting the use of immunomodulatory drugs, such as IL-6 inhibitors, but early experience suggests these drugs might be beneficial in improving outcomes in KTx patients with severe COVID-19.

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