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SHORT COMMUNICATION

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Management of immunosuppression in kidney transplant recipients with COVID-19 pneumonia: A summary of 41 confirmed cases reported worldwide

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Abstract

There is no consensus on immunosuppression management for kidney transplant recipients (KTRs) with SARS-CoV-2 pneumonia. Therefore, we conducted a search in English database from October 2019 to July 2020 and extracted data from cases with treatment details worldwide, and total of 41 recipients with a median age of 50 years were enrolled in this study. Most of them were males (75.8%). The most common presenting symptoms were fever (80.5%), cough (63.4%), and fatigue (41.5%). Patients were classified into three catalogs according to severity of pneumonia: 17 (41.5%) were mild, 15 (36.6%) severe, and 9 (21.9%) critical disease. Laboratory tests revealed that serum creatinine of critical patients was significantly higher than that of mild or severe patients. 68.3% received oxygen support; all patients received antiviral therapy, and 15 (36.6%) recipients were additionally treated with intravenous immunoglobulin and interferon-α. 19.5% of patients maintained immunosuppressive therapy; 36.6% suspended antimetabolite; and 43.9% only treated with corticosteroid. Six (14.6%) patients died (severe: 2, critical: 4); high creatinine with low lymphocyte count was the biggest challenge of immunosuppression management. In all, it is necessary to pay close attention to renal function and lymphocyte count in KTRs infected with COVID-19 and choose appropriate medication programs according to the specific situations.

KEYWORDS
COVID-19, immunosuppression management, kidney transplant recipient

1 | INTRODUCTION

With the increasing of cases of COVID-19 pneumonia around the world, reports recently revealed that kidney transplant recipients (KTRs) are more likely to be infected with SARS-CoV-2 under the same exposure conditions because of long-term immunosuppressive therapy. Large-scale reports found that the mortality rate of KTRs infected with SARS-CoV-2 was 24%-28%, significantly higher than that of nontransplant patients (1.4%-4.3%).[1,2] Many reports showed that patients with COVID-19 were prone to develop

Abbreviations: CNI, calpain inhibitors; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CsA, cyclosporin A; HCQ, hydroxychloroquine; IVIg, intravenous immunoglobulin; KTRs, kidney transplant recipients; MMF, mycophenolate mofetil; MP, methylprednisolone; MPA, mycophenolic acid; Pred, prednisone; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Tac, tacrolimus.

Qianchao Hu and Zibiao Zhong contributed equally to this work.

lymphocytopenia, and lymphocytopenia was related to the severity of patients.[3,4] Therefore, reduction or cessation of immunosuppressants seems to contribute to the increase of lymphocytes count in KTRs infected with SARS-CoV-2. However, reducing the usage of immunosuppressants increased the risk of kidney rejection. So far, there is no clear consensus to manage immunosuppressive therapy. Therefore, how to manage immunosuppressive therapy has become a crucial problem in KTRs with COVID-19.

In this review, we conducted a search in English database and extracted data from cases with treatment details worldwide and analyzed the relationship between the immunosuppressive regimen and the relevant indicators of KTRs with COVID-19, to provide an effective treatment plan for KTRs with SARS-CoV-2 pneumonia.

2 | MATERIALS AND METHODS

We carried out an electronic search in Medline (PubMed interface), Scopus, and Web of Science, using the keywords "COVID-19" OR "2019-nCoV" OR "SARS-CoV-2" OR "coronavirus 2019," AND "Transplant" OR "transplantation" OR "transplant recipients," AND "kidney" OR "renal," between October 1, 2019, and July 1, 2020. The reference list of all identified documents was scrutinized with the aim of identifying additional potentially eligible studies. Selection criteria were as follows: (a) Adult KTRs were diagnosed with SARS-CoV-2 infection; (b) more than 3 months after kidney (single organ) transplantation; (c) specific drug regimens of immunosuppressant; and (d) explicit clinical outcome (recovery or death). All references were assessed and selected by two independent reviewers (Qianchao Hu and Zibiao Zhong), and data were extracted from each study. Any disagreements arising during the selection assessment were resolved by discussion and consensus.

Information on sex, age, severity, renal function, lymphocyte number, immunosuppressant adjustment program, and clinical results of these 41 patients were collected and systematically reviewed the specific adjustment program of immunosuppressant in KTRs infected with SARS-Cov-2.

Statistical analysis was performed with SPSS V.17.0 software (IBM). Categorical data were presented as proportions, and continuous data were presented as means and SDs. Differences in proportions were tested by the chi-square tests. The continuous variables with a normal distribution were tested using Student's *t* test or analysis of variance test, and the continuous variables with a skewed distribution were tested using Mann-Whitney *U* test or the Kruskal-Wallis analysis. For all statistical tests, $P < .05$ was significant.

3 | RESULTS

3.1 | Clinical characteristics of all patients

A total of 21 reports were screened,[5-25] and 41 KTRs with laboratory-confirmed COVID-19 were enrolled.

Among these 41 cases, 31 (75.61%) were males and 10 (24.39%) were females. The median age was 50 (IQR: 37, 64) years. The common clinical symptoms of these patients included fever (80.5%), cough (63.4%), and fatigue (41.5%). Some of them had gastrointestinal symptoms (21.9%) and conjunctivitis (2.5%). The time from onset to admission was 8.4 (CI 5.5-11.3) days; 6 (14.6%) patients died during hospitalization while 35 survived. In addition, 31 (75.6%) patients received triple maintenance immunosuppressive therapy with calpain inhibitors (CNI) (tacrolimus or cyclosporin A), antimetabolites (mycophenolate mofetil or mycophenolic acid), and corticosteroids (prednisone or methylprednisolone), 1 (2.4%) special case used belatacept instead of CNI, and 9 (21.9%) received dual immunosuppressive therapy regimen (Table 1).

3.2 | Clinical features of different subtypes (Mild vs Severe vs Critical)

COVID-19 was classified according to the Guidelines for the Diagnosis and Treatment of COVID-19 (7th).[26] In a total of 41 cases, mild cases were identified in 17 (41.5%), severe cases in 15 (36.6%), and critical cases in 9 (21.9%). There were significant differences between the three groups in terms of age ($P = .042$), while no significant differences in admission time ($P = .198$) and hospital stay ($P = .788$; Table 2). The laboratory findings showed that there were no significant differences between the three groups in terms of lymphocyte count and C-reactive protein (CRP), while serum creatinine (Cr) in critical cases was significantly higher than mild or severe cases (Cr: 132.55 vs 163.17 vs 244.82, $P < .024$). And there was higher mortality in critical cases than other two subtypes (0% vs 13.3% vs 44.4%; Table 3).

3.3 | Treatments in different subtypes (Mild vs Severe vs Critical)

All patients received antiviral treatment, and common antiviral drugs were lopinavir/ritonavir, hydroxychloroquine (HCQ), oseltamivir, and umifenovir. Some patients additionally treated with intravenous immunoglobulin (IVIg, 34.1%) or interferon-α (INF-α, 9.8%). 68.3% patients received oxygen support. From Table 4, 35.5% mild cases received oxygen therapy, while in other subtypes the proportion reached to 93.3% and 88.9%, respectively.

As for the adjustment of immunosuppression, approach A: maintained on immunosuppression; approach B: only antimetabolites were suspended; approach C: only maintained on corticosteroids. From Table 4, the application proportion of approach A treatment in different subtypes were 41.2% vs 6.7% vs 0, approach B were 29.4% vs 40% vs 44.4%, and approach C were 29.4% vs 53.3% vs 55.6%. The death rate of patient who applied approach A was 0, approach B was 13.3%, and approach C was 22.2% (Table 4).

TABLE 1 Demographics, clinical characteristics, and symptoms at presentation in 27 kidney transplant recipients diagnosed with COVID-19

Case		Sex/Age	Major comorbidities	Immunosuppression regimen	Symptoms at presentation	Onset to admission (d)	Outcomes/d
Zhong, ZZ[5]	**1**	M/48	Peripheral blood tri-system reduction	Tac + MMF	Fever, cough, short of breath, fatigue	45	Recovery/60
Zhu L[6]	**2**	M/52	-	Tac + MMF + Pred	Fever, fatigue, dyspnea, nausea, cough	7	Recovery/28
Huang JF[7]	**3**	M/58	-	MMF + steroid	Fever, cough, shortness of breath	3	Death/40
Wang JP[8]	**4**	M/49	DM, HTN	CsA + MMF + Pred	fever and respiratory symptoms	7	Recover/14
Marx, D[9]	**5**	M/58	-	Belatacept + MMF + Pred	fever, mild dyspnea, and cough	2	Recovery/24
Bartiromo, M[10]	**6**	F/36	-	Tac + MP	Gastrointestinal symptoms, dry cough	5	Recovery/9
Zhang, H[11]	**7**	M/38	-	Tac + MMF + glucocorticoids	Fever, cough	11	Recovery/31
	8	F/37	HTN	Tac + MMF + glucocorticoids	Fever, cough	2	Recovery/30
	9	M/38	DM, HTN	Tac + MMF + glucocorticoids	Fever, cough, fatigue rhinorrhea	5	Recovery/27
Chen, S[12]	**10**	M/49	HTN	Tac + MMF + Pred	Fever, poor appetite	6	Recovery/34
Seminari, E[13]	**11**	M/50	DM, HTN	Tac + MMF	Fever, cough	9	Recovery/13
Fernández-Ruiz M[14]	**12**	M/78	HTN, PC	Tac + Pred	Fever, shortness of breath	1	Death/5
	13	M/71	HTN	Tac + Pred + MPA	Fever, shortness of breath, cough, sore throat	7	Death/16
	14	M/76	HTN, obesity	MMF + Pred + Rapamycin	Fever, rhinorrhea	3	Recovery/13
Arpali, E[15]	**15**	M/28	TTM	Tac + MMF + Pred	Fevers, malaise, sore throat, rhinorrhea	2	Recovery/14
Bussalino, E[16]	**16**	M/32	HTN	Tac + MPA + Pred	Fever, dyspnea, dry cough	3	Recovery/15
Ning, L[17]	**17**	M/29	HTN	MMF + CsA + MP	Fatigue, chills	2	Recovery/13
Zhu L[18]	**18**	M/24	-	Tac + MMF + Pred	Fever	27	Recovery/43
	19	M/55	CAD, AF, CHF	Tac + MMF + Pred	Cough, short of breath, fatigue	5	Recovery/48
	20	M/29	-	Tac + MMF + Pred	Fever, cough, short of breath, fatigue, diarrhea	7	Recovery/37
	21	M/30	HTN	Tac + MMF + Pred	Fever, cough, short of breath, fatigue	21	Recovery/37
	22	M/50	HTN	Tac + MMF + Pred	Fever, cough, short of breath, fatigue	11	Recovery/34
	23	M/52	HTN, CAD	Tac + MMF + Pred	Fever, cough, short of breath, fatigue	7	Recovery/20
	24	M/49	-	Tac + MMF	Fever, cough, short of breath, fatigue, diarrhea	9	Recovery/34

(Continues)

TABLE 1 (Continued)

Case		Sex/Age	Major comorbidities	Immunosuppression regimen	Symptoms at presentation	Onset to admission (d)	Outcomes/d
	25	M/59	HTN, HHD, COPD	CsA + Mizoribine	Fever, cough, short of breath, fatigue	8	Death/14
	26	F/37	HTN	Tac + MMF + Pred	Fever, cough, short of breath, fatigue	10	Recovery/31
Kates, OS[19]	**27**	M/54	DM, HTN	Tac + MMF	Fever, cough, vomiting, diarrhea, and dyspnea	4	Recovery/13
Kocak, B[20]	**28**	F/28	-	Tac + MMF + Pred	Rhinorrhea, sore throat, malaise, fever	2	Recovery/27
	29	F/56	HTN	Tac + MMF + Pred	Diarrhea, fever	3	Recovery/20
Fung, M[21]	**30**	M/47	DM, HTN, CVD	Tac + MMF + Pred	Fever, cough, dyspnea, myalgia	14	Recovery/39
	31	M/73	CAD, DM, HTN	Tac + MMF	Fever, cough, dyspnea, fatigue, diarrhea, anosmia, dysgeusia	21	Recovery/34
	32	M/77	CAD, sarcoidosis	Tac + MMF + Pred	Fever, Fatigue	2	Recovery/32
	33	F/71	CAD, DM, CVD	Tac + MMF + Pred	Fever, cough, fatigue, anosmia, dysgeusia	14	Recovery/21
Cheng DR[22]	**34**	M/48	-	Tac + MMF + Pred	Fever, chest tightness, asthenia	13	Recovery/22
	35	F/65	-	Tac + MMF + Pred	Fever, cough, chest distress muscle ache weakness	4	Recovery/41
Tantisattamo, E[23]	**36**	F/55	Hyponatremia	Tac + MMF+Pred	Cough, dyspnea, headache, decreased appetite, nausea, fatigue.	7	Recovery/12
Chen, D[24]	**37**	M/29	-	Tac + MMF + Pred	Fever, dry cough	2	Recovery/32
Maritati, F[25]	**38**	F/63	HTN, obesity	Tac + MPA + Pred	-	-	Death/11
	39	M/73	HTN, DM,	Tac + MPA + Pred	-	-	Recovery/34
	40	M/72	HTN, HHD, obesity	Tac + mTORi + Pred	-	-	Death/48
	41	F/71	HTN, ICD	Tac + MPA + Pred	-	-	Recovery/32

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CsA, cyclosporin A; CVD, cerebrovascular disease; DM, diabetes mellitus; F, female; HHD, hypertensive heart disease; HTN, hypertension; ICD, ischemic cardiac disease; M, male; MMF, mycophenolate mofetil; MP, methylprednisolone; MPA, mycophenolic acid; mTORi, mTOR inhibitor; PC, prostatic carcinoma; Pred, prednisone; Tac, tacrolimus; TTM, transient thrombotic microangiopathy.

TABLE 2 Vital signs and radiological characteristics at presentation, therapeutic approaches, management of immunosuppression and outcomes

Case	Severity	Renal function	Lymphocyte	IL-6	CRP	Antiviral therapy	Oxygen support	Immunosuppression adjustment	Outcomes/d
1	Mild	Normal	$0.5*10^9$/L	13.29 pg/mL	101.79 mg/L	Oseltamivir, INF-a, IVIg	Nasal cannula	Tac (maintained) + MMF (cessation) + MP	Recovery/60
2	Severe	Cr: 139 μmol/L	$1.13*10^9$/L	19.53 pg/mL	54.0 mg/L	Umifenovir, INF-a, IVIg	Oxygen inhalation	Tac (reduction) + MMF and Pred (cessation) + MP	Recovery/28
3	Critical	Renal failure	$0.38*10^9$/L	-	-	Lopinavir/ritonavir	Mechanical ventilation	MMF (cessation) + MP	Death/40
4	Mild	Normal	$0.59*10^9$/L	-	22.73 mg/L	Lopinavir/ritonavir, INF-a,	Nasal cannula	maintained on immunosuppression + MP	Recovery/14
5	Mild	Cr: 175 μmol/L	$0.5*10^9$/L	29 ng/L	88 mg/L	antiviral therapy	-	Belatacept and MMF (cessation) + Pred	Recovery/24
6	Severe	Cr: 202.5 μmol/L	normal	normal	67 mg/L	Darunavir/cobicistat, HCQ	-	Tac (high level in the blood) + MP	Recovery/9
7	Mild	Cr: 98.0 μmol/L	$0.63*10^9$/L	-	6.68 mg/L	Oseltamivir or umifenovir	-	Tac (reduction) + MMF (cessation) + corticosteroid	Recovery/31
8	Mild	Cr:137 μmol/L	$0.31*10^9$/L	-	9.77 mg/L	Oseltamivir or umifenovir, IVIg	-	Tac and MMF (cessation) + corticosteroid	Recovery/30
9	Mild	Cr: 135.4 μmol/L	$0.91*10^9$/L	-	33.72 mg/L	Oseltamivir or umifenovir	-	Maintained on immunosuppression	Recovery/27
10	Severe	Cr: 167.3 μmol/L	$0.43*10^9$/L	-	74.34 mg/L	Umifenovir, Ribavirin, IVIg	Oxygen inhalation	Tac (reduction) + MMF and Pred (cessation) + MP	Recovery/34
11	Mild	Cr: 145.9 μmol/L	$0.6*10^9$/L	26.22 pg/mL	1.86 mg/L	Lopinavir/ritonavir, HCQ	-	Maintained on immunosuppression	Recovery/13
12	Critical	-	-	-	-	Lopinavir/ritonavir	High-flow oxygen therapy	Tac (reduction) + Pred	Death/5
13	Severe	-	-	7 pg/mL	-	Lopinavir/ritonavir, HCQ, IVIg	CPAP	Tac (reduction) + MPA and Pred (cessation) + MP	Death/16
14	Mild	-	-	-	-	HCQ	CPAP	Pred and rapamycin (maintained) + MMF (cessation) + MP	Recovery/13
15	Mild	Cr: 81.3 μmol/L	$0.3*10^9$/L	-	5.7 ng/L	Oseltamivir	-	Maintained on immunosuppression	Recovery/14
16	Severe	Cr: 229.9 μmol/L	17.8%	86.3 ng/L	90 mg/L	HCQ, oseltamivir	Nasal cannula	Maintained on immunosuppression	Recovery/15
17	Mild	Cr: 102 μmol/L	$1.01*10^9$/L	-	-	Lopinavir/ritonavir + IVIg	-	Maintained on immunosuppression	Recovery/13
18	Mild	Cr: 198 μmol/L	normal	-	30 mg/L	Antiviral therapy	Nasal cannula	Maintained on immunosuppression	Recovery/43
19	Critical	Cr: 308 μmol/L	$0.3*10^9$/L	-	80.5 mg/L	Antiviral therapy, IVIg	Noninvasive ventilation	Tac (reduction) + MMF (cessation) + Pred	Recovery/48
20	Severe	Cr: 251 μmol/L	$0.47*10^9$/L	-	118 mg/L	Antiviral therapy	Nasal cannula	MMF (cessation) + Tac and Pred (maintained) + corticosteroid	Recovery/37

(Continues)

TABLE 2 (Continued)

Case	Severity	Renal function	Lymphocyte	IL-6	CRP	Antiviral therapy	Oxygen support	Immunosuppression adjustment	Outcomes/d
21	Severe	Cr: 209 μmol/L	0.61*10^9/L	-	42.6 mg/L	Antiviral therapy + IVIg	Nasal cannula	MMF and Tac (cessation) + Pred (maintained) + corticosteroid	Recovery/37
22	Severe	normal	0.42*10^9/L	-	40 mg/L	Antiviral therapy + IVIg	Nasal cannula	MMF and Tac (cessation) + Pred (maintained) + corticosteroid	Recovery/34
23	Mild	normal	0.99*10^9/L	-	54 mg/L	Antiviral therapy + IVIg	Nasal cannula	MMF and Tac (cessation) + Pred (maintained) + corticosteroid	Recovery/20
24	Severe	normal	normal	-	49.7 mg/L	Antiviral therapy	Nasal cannula	MMF and Tac (cessation) + corticosteroid	Recovery/34
25	Critical	Cr: 467 μmol/L	0.44*10^9/L	-	100.5 mg/L	Antiviral therapy + IVIg	Noninvasive ventilation	Mizoribine and CsA (cessation) + corticosteroid	Death/14
26	Severe	Cr: 189 μmol/L	0.19*10^9/L	-	34.1 mg/L	Antiviral therapy + IVIg	Nasal cannula	MMF and Tac (cessation) + Pred (maintained) + corticosteroid	Recovery/31
27	Critical	Cr: 459 μmol/L	0.87*10^9/L	-	-	HCQ	Nasal cannula	MMF (cessation) + Tac (reduction) + Pred	Recovery/13
28	Mild	Cr: 81.3 μmol/L	0.3*10^9/L	-	5.7 ng/L	Oseltamivir	-	Maintained on immunosuppression	Recovery/27
29	Mild	Cr: 199.7 μmol/L	0.7*10^9/L	-	76.1 ng/L	HCQ		MMF and Tac (cessation) + Pred (maintained)	Recovery/20
30	Critical	Cr: 97.2 μmol/L	0.7*10^9/L	-	176.9 mg/L	-	Ventilation	MMF (maintained) + Tac (maintained) + Pred (cessation)	Recovery/39
31	Mild	Cr: 93.7 μmol/L	1.48*10^9/L	-	48.6 mg/L	-	-	Tac (decreased) + MMF (cessation)	Recovery/34
32	Critical	Cr: 283.8 μmol/L	0.73*10^9/L	-	35.6 mg/L	-	-	Tac and Pred (cessation) + MMF	Recovery/32
33	Severe	Cr: 72.5 μmol/L	0.08*10^9/L		22.6 mg/L	-	Oxygen therapy	Tac + MMF (decreased) + Pred	Recovery/21
34	Severe	Cr: 112.3 μmol/L	1.12*10^9/L		49.68 mg/L	-	Oxygen therapy	Tac and MMF (cessation) + Pred	Recovery/22
35	Critical	Cr: 55.7 μmol/L	0.72*10^9/L		40.14 mg/L	IVIg	Ventilator	MP	Recovery/41
36	mild	Cr: 70.7 μmol/L	0.5*10^9/L	<5 pg/mL	0.8 mg/L	HCQ	-	Tac + MMF (cessation) + Pred	Recovery/12
37	severe	Cr: 138 μmol/L	0.61*10^9/L	-	38.6 mg/L	INF-a	Oxygen therapy	Tac + MMF (cessation) + Pred	Recovery/32
38	severe	Cr: 150.28 μmol/L	0.73*10^9/L	964 pg/mL	23 mg/L	HCQ, tocilizumab	CPAP	Tac and MPA (cessation) + Pred	Death/11
39	mild	Cr: 203.3 μmol/L	0.96*109/L	2.7 pg/mL	4.8 mg/L	Tocilizumab	Venturi mask	Tac and MPA (cessation) + Pred	Recovery/34
40	Critical	Cr: 265.2 μmol/L	0.42*109/L	141 pg/mL	8.1 mg/L	HCQ, lopinavir/ritonavir, tocilizumab	CPAP	Tac and mTORi (cessation) + Pred	Death/48
41	severe	Cr: 97.2 μmol/L	0.5*109/L	6.7 pg/mL	6 mg/L	HCQ, IVIg, tocilizumab	CPAP	Tac and MPA (cessation) + Pred	Recovery/32

Abbreviations: CPAP, continuous positive airway pressure; CRP, C-reactive protein; CsA, cyclosporin A; HCQ, hydroxychloroquine; IFN-a, interferon-a; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MP, methylprednisolone; MPA, mycophenolic acid; mTORi, mTOR inhibitor; Pred, prednisone; Tac, tacrolimus.

TABLE 3 Clinical features of COVID-19 with different subtypes

Parameters	Mild cases (n = 17)	Severe cases (n = 15)	Critical cases (n = 9)	Two-tailed *P* value
Man, n (%)	13 (76.4%)	10 (66.7%)	8 (88.9%)	-
Age (mean, y)	47.8 ± 16.441	47.8 ± 15.588	62.8 ± 10.883	**.042**
Admission time (mean, d)	9.69 ± 11.85	8.85 ± 5.10	4.20 ± 2.59	.198
Laboratory findings				
Cr (mean, μmol/L)	132.55 ± 48.60	163.17 ± 54.81	244.82 ± 147.89	**.024**
Lymphocyte (mean, 10^9/L)	0.685 ± 0.329	0.572 ± 0.330	0.75 ± 0.208	.564
CRP (mean, mg/L)	32.68 ± 33.74	50.69 ± 29.18	73.62 ± 60.49	.085
Hospital stay (mean, d)	22.6 ± 13.74	24.7 ± 11.15	26.5 ± 14.01	.788
Death in hospital stay, n (%)	0	2 (13.3%)	4 (44.4%)	-

The bold values means that compared with the Age and Cr of Critical cases, that of Mild cases and Severe cases are significantly low.

TABLE 4 Treatment in COVID-19 with different subtypes

Parameters	Mild cases (n = 17)	Severe cases (n = 15)	Critical cases (n = 9)	Death, n (%)
Oxygen support (%)	6 (35.3%)	14 (93.3%)	8(88.9%)	-
Immunosuppression adjustment				
Approach A, n (%)	7 (41.2%)	1 (6.7%)	0	0
Approach B, n (%)	5 (29.4%)	6 (40%)	4 (44.4%)	2 (13.3%)
Approach C, n (%)	5 (29.4%)	8 (53.3%)	5 (55.6%)	4 (22.2%)
Death, n (%)	0	2 (13.3%)	4 (44.4%)	-

3.4 | Novel strategy to classify KTRs with COVID-19 (Type I vs Type II vs Type III vs Type IV)

The KTRs with COVID-19 were classified into four types according to Cr and lymphocyte count as shown in Table 5. We first explored differences among those four types in management of immunosuppression. From Table 5, there was higher mortality in type IV cases than other three types (0 vs 0 vs 0% vs 40%), and all the death cases were included into type IV. Moreover, the mortality in type IV cases treated with approach A was 0/0, approach B was 2/6, and approach C was 4/9 (Table 5).

4 | DISCUSSION

As of July 7, 2020, the total number of confirmed cases of COVID-19 in the world has reached 11.5 million, and the number of daily new cases has not shown a downward trend.[27] For the high infectivity of SARS-CoV-2 and the immunosuppressive state, KTRs were more vulnerable to the influence by COVID-19 than general population under the same exposure conditions. The mortality rate of KTRs with COVID-19 was also significantly higher than that of the general population.[1] Therefore, we collected such literature and carried out statistical analysis trying to find the reasonable basis for management of immunosuppression.

These data showed that 41 patients we collected were mainly male (75.6%), with a median age of 50 (IQR: 37, 64) years. The initial symptoms were fever, cough, and fatigue, and some patients had digestive system symptoms, like the general population. The severity of patients was divided into mild (41.5%), severe (36.6%), critical (21.9%). The incidence of severe disease was higher than that of the general population.[28] Although the mortality rate was 14.6%, <20%-50% in previous reports, it was significantly higher than the general population.[29]

Although there was no specific drug to fight against COVID-19, taking antiviral drugs and general treatment was the best expedient.

TABLE 5 Novel strategy to classify KTRs with COVID-19

Parameters	Type I (n = 8)	Type II (n = 14)	Type III (n = 4)	Type IV (n = 15)	Death (n)
Classification criteria					
Cr (μmol/L)	<150	<150	≥150	≥150	-
Lymphocyte (10^9/L)	≥0.9	<0.9	≥0.9	<0.9	-
Laboratory findings					
CRP (mean, mg/L)	48.28	56.18	62.33	67.274	-
Severity					
Mild (n)	5	8	2	2	0
Severe (n)	3	4	2	6	2
Critical (n)	0	2	0	7	4
Immunosuppression adjustment					
Approach A (n)	2	4	2	0	0
Approach B (n)	3	5	1	6	2
Approach C (n)	3	5	1	9	4
Death, n (%)	0	0	0	6 (40%)	-

The main antiviral drugs were lopinavir/ ritonavir, HCQ, and umifenovir, and some patients were treated additionally with IVIg (34.1%) and INF-α (9.8%). Previous studies reported that HCQ can effectively fight against SARS-Cov-2,[30] but in the cases we collected, it did not show significant efficacy. In addition, It was reported that lopinavir/ ritonavir could interact with tacrolimus (Tac).[10] Therefore, we should pay close attention to the blood concentration of Tac when giving lopinavir/ritonavir to KTRs, to prevent the occurrence of adverse events caused by high concentration of Tac. Additionally, those cases we collected showed that using IVIg or INF-a did not improve the prognosis of patients. Oxygen therapy was an important measure to improve the patient's respiratory function. Those cases showed that for mild patients, if they have shortness of breath or dyspnea, nasal cannula should be given; for severe and critical patients, they could be given mechanical ventilation, even extracorporeal membrane oxygenation (ECMO).

There were three immunosuppressive regimens for 41 renal transplant recipients. And the adjustment of immunosuppression was divided into 3 approaches. The results showed that the mortality of approach A was 0, the mortality of approach B was 13.3%, and the mortality of approach C was 22.2%. Further analysis found that the patients treated with approach A were mainly mild patients, indicating that approach A was the best choice for mild cases of KTRs; however, it is too hasty to confirm that approach A applies to all patients.

For the management of immunosuppression for severe and critical cases, we divide patients into four types, as shown in Table 5. Types I and II were mostly mild patients, and therefore, approach A was suitable for those two types of cases. Notably, type II cases suspended antimetabolites, because antimetabolites can significantly inhibit lymphocyte proliferation, and cessation of antimetabolites would help to alleviate peripheral blood lymphocytes depletion. Previous reports showed that after mycophenolate mofetil (MMF) was stopped, the patient who suffered peripheral blood trisystem reduction was eventually cured.[5] Thus, type II cases should apply approach B when they were also classified into severe patients. Types III and IV were mostly severe and critical patients. The reasons for the deterioration of renal function of types III and IV patients were virus invading and inflammatory response in kidney, which induced lymphocytes to aggregate into renal tissue. Therefore, we recommend that immunosuppressive therapy should not be changed for the type III patients, because maintaining on immunosuppressive therapy could mitigate excessive inflammatory response. If type III patients continued to deteriorate, they would become type IV. These patients have respiratory failure, lymphocyte depletion, and renal failure at the same time. The risk of death in type IV patients was very high, and this was the biggest challenge for KTRs infected with SARS-CoV-2. In order to maintain the patient's life, mechanical ventilation and renal replacement therapy were important measures. At same time, antimetabolites should be stopped due to lymphocyte depletion; CNI and corticosteroids should be maintained against the cytokine storm. Previous studies suggested that only application of corticosteroids in type IV cases could not reverse the patient's condition.[7,18]

We summarized the treatment details of 41 patients in the world and concluded a set of immunosuppression adjustment scheme in this article, hoping to provide adjustment basis for clinicians. However, due to the small number of cases, the author's subjectivity may exist in these reports, which makes our samples biased. Therefore, we call for more clinical reports to focus on the specific adjustment plan of these four types of patients and finally solve the problem of immunosuppressive adjustment.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

HQC and ZZB designed and carried out the research, analyzed the data, and wrote the manuscript. XY, YSJ, and WYF provided guidance and revised the manuscript. YQF designed the experiments, provided overall guidance, and helped to write the manuscript.

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