











ORIGINAL REPORT

Low rate of COVID-19 pneumonia in kidney transplant recipients—A battle between infection and immune response?

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Abstract

Background: With COVID-19 pandemic, concerns about kidney transplant recipients are rising. However, the incidence, clinical course, outcome, and predictive factors of disease severity are obscured.

Methods: We describe clinical and laboratory manifestations, radiologic findings, clinical course, and finally outcome of kidney transplant recipients with COVID-19 pneumonia.

Results: Of 2493 kidney transplant recipients under follow-up in our clinic, 19 cases (4 cases diagnosed based on radiologic findings) were admitted. The mean age of patients was 47.6 ± 12.4 years, and the mean time from transplantation was 115.6 ± 70.3 months. Lymphopenia and eosinopenia were 84.2% and 78.9%, respectively. Nine patients did not survive the hospital course. History of acute rejection during the past 12 months, diabetes, higher N/L ratio, lower platelet count, elevated N/L x CRP, higher levels of LDH, positive D-dimer, higher troponin, and prolonged PT were associated with mortality. Among patients with positive COVID-19 test, history of acute rejection, low platelet count, and positive D-dimer were associated with poor outcome. Treatment with cyclosporine was associated with better clinical outcome.

Conclusions: Low rate of admission in transplant recipients specially in the very first years of transplantation might be due to protective effects of immunosuppressive agents against cytokine storm or modification of immunity function. We suggest evaluation of T-cell number, function, and cytokine profile as a guide to manage COVID-19 mainly in patients with higher risk of mortality.

KEYWORDS

COVID-19, cytokine storm, immunosuppressive, kidney transplantation, N/L ratio

Abbreviations: ARBs, Angiotensin receptor blockers; CNI, calcineurin inhibitor; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; MDRD, modification of diet in renal disease; MMF/MPA, mycophenolate mofetil/mycophenolic acid; N/L ratio, neutrophil to lymphocyte ratio; PLT/Lymph, platelet to lymphocyte ratio.

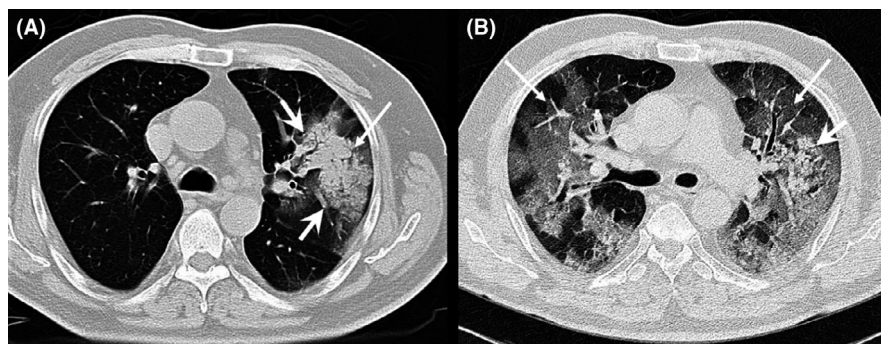


FIGURE 1 Fifty nine-year-old man with dry cough, fever, and history of three years kidney transplantation. A, CT images obtained on the day of admission show unilateral consolidation (*wide arrows*) with inside air bronchogram and ground-glass (*long arrows*) opacities in left upper lobe. B, Follow-up CT images (4 d later) show extensive bilateral ground-glass and consolidation opacities. Patient passed away after 17 d of hospitalization

1 | INTRODUCTION

Following the outbreak of novel corona virus infection (COVID-19) in the late December 2019 in China and its spread throughout the world, the disease was first reported in Iran on 20th of February 2020. Since then more than 85 000 have been diagnosed and 5297 had lost their lives in the country. (By April 22nd, 2020).

According to the literature, older patients and those with comorbidities such as diabetes, hypertension, cardiovascular diseases, obesity, and immunosuppressed patients are at higher risk of morbidity and mortality.¹ Kidney transplant recipients are in a chronic immunosuppressive state, which theoretically might pose them to the higher risk of complications, uncommon presentations, and worse outcome comparing with general population. Nevertheless, the incidence, clinical course, and outcome of COVID-19 are not clear in this population.

The aim of our study was to report clinical manifestations, laboratory findings, disease course, and outcome of 19 kidney transplant recipients who were admitted in Labbafinejad Medical Center from 20th February 2020 till 15th of April 2020.

2 | METHODS AND MATERIALS

In Labbafinejad Medical Center, we perform around 200 kidney transplantation per year (nearly 60% of them from deceased donors). Of 2493 patients that are currently followed by active clinical or phone surveillance, 19 kidney transplant recipients were admitted with the diagnosis of COVID-19 from 20th February 2020 till 15th of April 2020.

We described the clinical and laboratory manifestations, radiologic findings, clinical course, and outcome of these patients. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences. (Ethical Code: IrSBMU.MSP.REC.1399.003).

All adult kidney transplant recipients who were admitted to our center were enrolled. Oro- or nasopharyngeal swabs were taken at presentation. Demographic data including age, gender, comorbidities, graft characteristics, and maintenance immunosuppressive therapy were extracted from patients' files. History of treatment

for acute rejection episode during the past 12 months was registered. Clinical presentations and laboratory and radiologic findings were recorded. Laboratory assessments consisted of complete blood count, and differential cell count, serum creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), serum albumin, ferritin, troponin, D-dimer, coagulation testing, C-reactive protein (CRP), lactate dehydrogenase (LDH), creatine kinase (CPK), and pH. Bacterial infections were ruled out by taking blood and urine cultures. IL-6 and fibrinogen were assessed. Allograft function was evaluated by creatinine-based MDRD equation of eGFR.

Initial chest CT scans were interpreted by two independent radiologists. Predominant pattern of involvement, percentage of the lobar involvement, extension of involvement (Unilateral/ Bilateral), total lung score, and percentage of lung involvement were reported (Figure 1).

Clinical course, ICU admission, type of ventilatory support, vasopressor requirement, and the outcome of hospitalized COVID-19 patients were evaluated. Outcomes considered as admission to an intensive care unit, death, or discharge from the hospital.

Patients were treated according to the protocol with antiviral treatment and immunosuppressive dose reduction (discontinuation of antimetabolites, CNI dose reduction in normoxemic patients and discontinuation among hypoxemic patients), prednisolone 20 mg daily or methylprednisolone 40 mg daily in normoxemia and hypoxemic patients, respectively, and IVIG 1-2 g/kg over 5 days in hypoxemic patients.² The antiviral therapy dosing was as followed: (a) hydroxychloroquine 200 mg twice daily in patients who were not treated with lopinavir/ritonavir, and 400 mg on day one in those treated with lopinavir/ritonavir; (b) lopinavir/ritonavir 400/100 mg twice daily; (c) favipiravir 1600 mg on day one and then 600 mg twice daily; (d) oseltamivir 75 mg twice daily (adjusted based on eGFR); and (e) ribavirin 1200 mg twice daily (adjusted based on eGFR). The duration of treatment was 7-10 days.

3 | RESULTS

Out of about 2500 kidney transplant recipients under follow-up in our center, only 19 patients were admitted with diagnosis of

COVID-19 based on positive pharyngeal swab (15 patients) or compatible CT scan findings (four patients).

3.1 | Demographic and clinical manifestations

Patients' demographic and clinical manifestations are demonstrated in Table 1. The mean age of patients was 47.6 ± 12.4 years, with the youngest 29 and the oldest 66 years old. 13 (68.4%) of the cases were male.

Eight (42.1%) patients had received kidney transplantation from deceased donors. All patients except 5 (26.3%) had their first kidney allograft. The mean time passed from transplantation was

115.6 ± 70.3 (24 to 240) months. None of our patients with COVID-19 was diagnosed in the first 2 years after transplantation.

Only three allograft recipients had been treated with plasmapheresis, IVIG, and rituximab for chronic active antibody-mediated rejection during the past 12-month prior to admission. Two of them experienced rejection within a month of COVID-19 infection and one, 6 months earlier.

Maintenance immunosuppressive regimen was cyclosporin, MMF/MPA and prednisolone in 9 (47.4%), tacrolimus, MMF/MPA and prednisolone in 7 (36.8%), and sirolimus, MMF/MPA and prednisolone in 3 (15.8%). About 58% of our cases were treated with angiotensin receptor blockers (ARBs).

Characteristics	All patients (N = 19)	Hospital course		P value
		Death (N = 9)	Alive (N = 10)	
Age (mean \pm SD), y	47.6 (12.4)	51.2 (12.8)	44.3 (11.8)	.24
Male sex—no (%)	13 (68.4)	8 (88.9)	5 (50.0)	.24
Diabetes	4 (21.1)	3 (33.3)	1 (10.0)	.05
Hypertension	6 (31.6)	2 (22.2)	4 (40.0)	.21
Glomerulonephritis	-			.43
Diabetes mellitus	4 (21.1)	3 (33.3)	1 (10.0)	
Nephroangiosclerosis (HTN)	4 (21.1)	2 (22.2)	2 (20.0)	
Polycystic kidney disease	2 (10.5)	0 (0)	2 (20.0)	
Uropathy	4 (21.1)	2 (22.2)	2 (20.0)	
Other or undetermined	5 (26.3)	2 (22.2)	3 (30.0)	
Deceased Donation—no (%)	8 (42.1)	2 (22.2)	6 (60.0)	.09
Second kidney transplant—no (%)	5 (26.3)	2 (22.2)	3 (30.0)	.70
Baseline eGFR (mean \pm SD), cc/min	49.6 (21.6)	47.2 (26.5)	51.7 (17.2)	.84
History of acute rejection in past year, n (%)	3 (15.8)	3 (33.3)	0	.02
Dyspnea, n (%)	13 (68.4)	6 (66.7)	7 (70.0)	.88
Dry cough, n (%)	10 (52.6)	6 (66.7)	4 (40)	.24
Fever, n (%)	14 (73.7)	6 (66.7)	8 (80.0)	.51
Myalgia, n (%)	7 (36.8)	3 (33.3)	4 (40.0)	.76
Respiratory rate (mean \pm SD), /min	21.9 (3.5)	22.4 (4.4)	21.5 (2.5)	.78
Hypoxemia ($\text{SpO}_2 < 93\%$), n (%)	17 (89.5)	8 (88.9)	9 (90.0)	.94
Fever, n (%)	14 (73.7)	6 (66.7)	8 (80.0)	.51
Cyclosporin, n (%)	9 (47.4)	2 (22.2)	7 (70.0)	.03
Tacrolimus, n (%)	7 (36.8)	5 (55.6)	2 (20.0)	.11
Sirolimus, n (%)	3 (15.8)	2 (22.2)	1 (10.0)	.47
MMF/ MPA, n (%)	18 (94.7)	9 (100.0)	9 (90.0)	.33
ARBs, n (%)	11 (57.9)	5 (55.6)	6 (60.0)	.84

TABLE 1 Demographic and clinical manifestations, according to patients' outcome

Abbreviations: ARBs, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; MMF/MPA, mycophenolate mofetil/mycophenolic acid.

TABLE 2 Laboratory findings of patients according to disease outcome

Variables	All patients (N = 19)	Hospital course		P value
		Death (N = 9)	Alive (N = 10)	
WBC, /mm ³ (mean ± SD)	5794.7 (2319.1)	6355.6 (2708.4)	5290 (1907.5)	.45
Neutrophil count/mm ³ (mean ± SD)	4759.1 (2327.1)	5477.8 (2696.1)	4112.2(1840.7)	.36
Lymphocyte count/mm ³ (mean ± SD)	829.6 (442.0)	722.6 (584.7)	925.9 (255.0)	.13
Lymphopenia, no (%)	16 (84.2)	7 (77.8)	9 (90.0)	.46
Eosinophil count/mm ³ (mean ± SD)	120.8 (85.0)	145.6 (99.6)	98.5 (67.0)	.24
Eosinopenia, no (%)	15 (78.9)	6 (66.7)	9 (90.0)	.21
N/L ratio (mean ± SD)	8.0 (6.2)	11.4 (7.2)	4.9 (2.8)	.03
Platelet count/mm ³ (mean ± SD)	156 736.8 (85 998.0)	107 000.0 (50 828.1)	201 500.6 (88 287.7)	.004
PLT/ lymph ratio (mean ± SD)	235.0 (178.7)	234.0 (172.2)	235.8 (193.6)	.98
CRP, mg/L (mean ± SD)	29.8 (13.9)	24.9 (13.9)	34.3 (12.9)	.28
Elevated CRP, n (%)	17 (89.5)	7 (77.8)	10 (100.0)	.07
N/L × CRP (mean ± SD)	225.6 (203.1)	292.7 (262.5)	165.2 (112.7)	.03
eGFR, cc/min (mean ± SD)	34.1 (19.5)	30.0 (22.1)	37.7 (17.2)	.40
SpO ₂	89.1 (3.3)	87.7 (3.9)	90.4 (2.1)	.05
AKI (%)	14 (73.7)	7 (77.8)	7 (70.0)	.70
AST U/L (mean ± SD)	39.5 (38.0)	47.4 (48.5)	32.4(25.8)	.45
ALT U/L (mean ± SD)	25.2 (27.3)	24.1 (27.4)	26.3 (28.7)	.90
CPK U/L (mean ± SD)	153.0 (180.6)	174 (226.1)	134.1 (137.7)	.78
LDH U/L (mean ± SD)	736.3 (552.3)	1014.3 (696.8)	486.1 (177.3)	.03
Elevated LDH (%)	11 (57.9)	7 (77.8)	4 (40.0)	.09
Albumin g/dL, (mean ± SD)	3.4 (0.4)	3.3 (0.3)	3.5 (0.4)	.28
Hypoalbuminemia (%)	10 (52.6)	6 (66.7)	4 (40.0)	.24
Ferritin ng/mL (mean ± SD)	473.2 (195.3)	479.7 (245.2)	470.0 (184.7)	.94
Troponin (mean ± SD)	0.0006 (0.0092)	0.0100 (0.120)	0.003 (0.003)	.04
IL-6(mean ± SD)	86.4 (90.9)	122.1 (101.6)	57.8 (80.6)	.32
Positive D-Dimer (%)	7 (36.8)	5 (55.6)	2 (20.0)	.002
Fibrinogen (mean ± SD)	440.3 (142.8)	406.2 (71.8)	467.6 (186.7)	.73
PT (mean ± SD)	11.7 (1.7)	12.5 (1.9)	11.1 (1.3)	.07
PTT (mean ± SD)	86.0 (26.9)	32.5 (21.1)	21.9 (2.6)	.13
INR (mean ± SD)	1.12 (0.19)	1.20 (0.22)	1.05 (0.12)	.08
Positive COVID-19 (%)	15 (78.9)	8 (88.9)	7 (70.0)	.31
PH	4.47 (7.31)	7.26 (0.10)	7.35 (0.06)	.04

Abbreviations: N/L, Neutrophil to lymphocyte ratio; PLT/Lymph, Platelet to lymphocyte ratio.

In the study population, 53% had comorbidities (21% diabetes, 32% hypertension).

The most common clinical manifestation at the onset of illness was fever (73.7%), followed by dry cough and dyspnea (68.4% and 52.6%, respectively). None of our cases had experienced gastrointestinal symptoms or anosmia. 89.5% of patients were hypoxemic (O₂ saturation < 93% at ambient air) at presentation.

3.2 | Laboratory findings

On the day of admission, 84.2% of patients had lymphopenia which was defined as lymphocyte count less than 1100 per mm³. Thrombocytopenia (platelet count less than 150 000 per mm³) was detected in 57.9% of patients. Besides, 78.9% of cases had

eosinopenia. Four of our patients had coagulopathy at the onset of the illness, with INR > 1.1.

Elevated LDH level (LDH > 480 U/L) was found in 58% of the cases, with the mean LDH level of 736.3 ± 552.3 U/L. Increased CRP (>10 mg/L), elevated ferritin (>300 ng/mL), and hypoalbuminemia (Albumin concentration < 3.5 g/dL) were detected in 89.5%, 83.3%, and 52.9% of cases, respectively.

Upon admission, 73.7% of patients had AKI which was defined as more than 30% decrease in eGFR from the baseline eGFR, based on MDRD equation.

Blood and urine cultures accompanying by CMV PCR were negative in all of the participants. More detailed laboratory findings are shown in Table 2.

3.3 | Radiologic findings

Fifteen patients underwent lung CT scan early in the course of disease. The images were interpreted by two radiologists, independently (Table 3).

Two-thirds of patients had bilateral lung involvement with either ground-glass opacities or consolidation or both. None of our cases had cavitation, cystic changes, and lymphadenopathy. Three patients had pleural or pericardial effusion or both. Sixteen patients with low-dose CT scan were followed up with portable X-ray. Progression in lung involvement was found in serial CXRs.

3.4 | Treatment

Treatment strategies were as followed: 13(68.4%) of patients were treated with CNI dose reduction while in 11 (57.9%) CNIs were discontinued. We stopped MMF/MPA and mTOR inhibitors in all admitted patients.

All the patients received antiviral drugs, including: 68.4% oseltamivir, 94.7% hydroxychloroquine, 78.9% lopinavir/ritonavir, and 78.9% ribavirin. Two patients were treated with favipiravir. One patient did not receive hydroxychloroquine during this hospital course since he was treated before in the outpatient setting. Fourteen patients received IVIG with total dose of 1-2 g/kg. Only one patient was treated with COVID-19 convalescent plasma. He was one of our

last patients who were admitted and discharged home with normal functioning graft. Two patients had underwent hemoperfusion with diagnosis of cytokine release syndrome, with an IL-6 level of 210 pg/mL (normal value < 16 pg/mL) and positive d-dimer; nonetheless none of them survived the course of COVID-19 pneumonia (Table 4).

3.5 | Clinical outcome

Of total 19 patients, 10 (52.6%) were admitted to ICU, 9 (47.7%) of them died due to the complications of COVID-19 pneumonia. Thirty percent needed NIV (noninvasive ventilation) followed by invasive mechanical ventilation. Mechanical ventilation administered in six patients initially and three patients following failure of NIV, and 80% of ICU patients needed vasopressor. Median length of stay in ICU was 11 days, and median time to death in ICU was 19 days. Three patients were treated with renal replacement therapy during their ICU admission.

Ten patients were discharged home, all with functioning graft, although two of them had some degrees of graft dysfunction comparing with their baseline graft function (22.34 vs 37.39 cc/min, and 42.84 vs 68.4 cc/min). In terms of their immunosuppressive treatment, all were discharged with low-dose CNI and prednisolone 10 mg daily, with the recommendation of close follow-up.

When comparing those who survived the hospital course with those who did not, history of acute rejection during the past 12 months (*P* value .02) and diabetes (*P* value .05) correlated with poor outcomes. When it comes to the maintenance immunosuppressive therapy, those who survived mostly were on cyclosporine (*P* value .03).

Patients who lost the battle with disease had higher N/L ratio (*P* value .03), lower platelet count (*P* value .004), elevated N/L \times CRP (*P* value .03), and higher levels of LDH (*P* value .03). Positive D-dimer (>0.5 μ g/mL), higher troponin, and prolonged PT, on admission predicted worse outcomes. These results pointed out that the activation of coagulation pathway and evidences of tissue injury on admission may lead to worse clinical outcome. Lower pH and Spo₂ at presentation indicated more severe disease and higher mortality rate.

Patients with unilateral lung involvement had superior outcome over those with bilateral lesions. Total lung involvement scores (ground-glass and/or consolidation patterns) were higher in

	All (N = 19)	Death (N = 9)	Alive (N = 10)	<i>P</i> value
GG score, mean \pm SD	6.9 (4.7)	9.1 (5.0)	4.4 (3.1)	.05
CC score, mean \pm SD	1.67 (1.67)	2.38 (2.00)	0.86 (0.69)	.07
Total involvement, mean \pm SD	8.6 (5.4)	11.5 (5.2)	5.3 (3.3)	.02
Total percent, mean \pm SD	43.0 (26.8)	57.5 (26.2)	26.4 (16.8)	.02
Unilateral lesion (%)	5 (25.3)	2 (22.2)	3 (30.0)	.46
Bilateral lesions (%)	10 (52.6)	6 (66.7)	4 (40.0)	

TABLE 3 Radiologic Findings of patients according to disease outcome

Abbreviations: CC, consolidation; GG, Ground- glass.

TABLE 4 Treatments and clinical outcome

Characteristics	All patients (N = 19)	Hospital course		P value
		Death (N = 9)	Alive (N = 10)	
CNI dose reduction (%)	13 (68.4)	5 (55.6)	8 (80.0)	.25
CNI discontinuation (%)	11 (57.9)	9 (100.0)	2 (20.0)	.0001
Oseltamivir (%)	13 (68.4)	7 (77.8)	6 (60.0)	.40
Hydroxychloroquine (%)	18 (94.7)	8 (88.9)	10 (100.0)	.28
Lopinavir/ritonavir (%)	15 (78.9)	9 (100.0)	6 (60.0)	.03
Ribavirin (%)	15 (78.9)	9 (100.0)	6 (60.0)	.03
IVIG (%)	14 (73.7)	9 (100.0)	5 (50.0)	.01
Transplant to admission (mo), mean, SD	115.6 (70.3)	105.3 (75.4)	124.8 (68.2)	.55
Rejection To admission (mo), mean, SD	1.68 (5.6)	0.89 (1.7)	2.4 (7.6)	.50
Symptom to admission (d), mean, SD	4.21 (3.7)	4.8 (4.8)	3.7 (2.4)	1.0
Total hospital stay (days), mean, SD	13.0 (9.0)	17.1 (7.7)	9.3 (8.8)	.008

Abbreviations: CNI, calcineurin inhibitor; IVIG, intravenous immunoglobulin.

non-survived patients (P value .02). As might be predictable, the more the involvement in CT scan, the higher was the mortality of patients.

3.6 | Subgroup analysis

We analyzed those patients with positive COVID PCR by omitting four patients with only radiologic diagnosis. Comparing the demographic, clinical, laboratory, and radiologic findings of patients who survived and those who did not, the results were as followed. History of acute rejection during the past 12 months (P value .03), lower platelet count (P value .008), and positive D-dimer (P value .04) were still associated with poor outcome. Treatment with cyclosporine was more common among those who survived the course of disease (P value .02). Male gender and high LDH levels were more common in those who did not survive, although not statistically significant (P value .06). The degree of CT scan lung involvement was greater among non-survivors. The results are displayed in Table 5.

4 | DISCUSSION

COVID-19 is a global health issue. It was speculated that older patients, and those with comorbidities such as hypertension and diabetes are at higher risk of complications and mortality.^{1,3} Among immunosuppressed kidney transplant recipients, data are scarce about COVID-19.

In our center with nearly 2500 kidney transplant recipients under follow-up, only 19 patients were admitted with the diagnosis of COVID-19 in a 2-month period, which suggests that transplant patients might not be at a higher risk of severe complications of the disease and the need for hospital admission.

Four patients had negative oropharyngeal swabs, which might be due to low sensitivity (60%-70%) of the test⁴; still, they had diagnostic CT scan findings compatible with COVID-19 pneumonia.⁵

There was a higher risk of mortality in patients with recent history of chronic active antibody-mediated rejection who were treated with Rituximab. It seems that anti-B-cell therapy might be associated with more severe disease, as noted in patients with multiple sclerosis and granulomatosis with polyangiitis.^{6,7} Diabetic transplanted patients as general population were at higher risk of complications and mortality.³

Lymphopenia, high CRP, hypoalbuminemia, and increased ferritin level were consistent with previous studies.^{1,8} Interestingly, about 79% of patients had eosinopenia upon diagnosis. This finding was consistent with data from Liu, et al that described eosinopenia in almost all the 10 patients in their study.⁸ This finding might be due to stress-induced secretion of steroids that inhibited marrow release of eosinophils. They demonstrated improvement of eosinophil count by disease recovery.

Nearly 73% of our cases had AKI at presentation, even before initiation of antiviral treatment. In various case series of patients with either transplanted or native kidneys, the incidence of AKI was about 40%.⁹⁻¹¹

The low incidence of disease could be on one hand due to respecting the social distancing rules by this group, or due to the fact that some levels of immunosuppression could protect them against the severe immunologic response, cytokine storm, and viral replication. Carbajo-Lozoya, et al reported back in 2012 that inhibition of FK506 and immunophilin pathway by non-toxic concentrations of Tacrolimus inhibits growth of coronaviruses such as SARS-COV.¹²

Meanwhile, as the disease course can be divided in three phases, namely, phase I early infection, phase II pulmonary involvement (IIa) without hypoxia and (IIb) with hypoxia, and phase III systemic hyper-inflammation,¹³ the optimal management of immunosuppressive

TABLE 5 Characteristics of patients with positive COVID-19 PCR results

Characteristics	Death (N = 8)	Alive (N = 7)	P value
Age (mean \pm SD), y	49.4 (12.4)	45.0 (9.4)	.46
Male sex—no (%)	7 (87.5%)	3(42.9%)	.06
Diabetes (%)	25%	0	.09
Deceased Donation—no (%)	66.7	33.3	.39
History of acute rejection in past year, (%)	37.5	0	.03
MMF/MPA (%)	100	85.7	.20
Cyclosporine (%)	12.5	71.4	.02
Lymphopenia (%)	75	100	.09
Eosinopenia (%)	75	85.7	.60
N/L ratio (mean \pm SD)	10.6 (7.3)	5.6 (2.9)	.11
N/Lx CRP (mean \pm SD)	275.9 (275.4)	199.2 (115.0)	.51
CRP, mg/L (mean \pm SD)	25 (14.8)	38.3(11.5)	.08
Platelet count/mm ³ (mean \pm SD)	97 000.0 (43 863.4)	216 428.6 (98 386.7)	.008
PT (mean \pm SD)	12.6 (2.0)	11.3 (1.4)	.19
Troponin (mean \pm SD)	0.010 (0.013)	0.003 (0.003)	.18
Fibrinogen (mean \pm SD)	406.25 (71.7)	538.7 (220.9)	.41
LDH (mean \pm SD)	1100.4 (962.0)	510.3 (186.1)	.048
Positive D-Dimer (%)	62.5	28.6	.04
Hypoalbuminemia (%)	75.0	49.9	.20
IL-6 (mean \pm SD)	122.1 (101.6)	89.3 (96.3)	.68
SPO2	88.0 (4.0)	90.1 (2.3)	.24
GG score, mean \pm SD	7.86 (3.76)	5.75 (2.87)	.36
CC score, mean \pm SD	2.43 (2.15)	1.00 (0.82)	.24
Total involvement in lung CT scan (mean \pm SD)	10.29 (4.27)	6.75 (2.99)	.18
Total percent of involvement in CT scan (mean \pm SD)	51.43 (21.35)	33.75 (14.93)	.18

Abbreviations: CC, consolidation; GG, ground-glass; MMF/MPA, mycophenolate mofetil/mycophenolic acid; N/L, neutrophil to lymphocyte ratio.

therapy remains unclear. It might be of use to treat patients with low-dose CNi in the late phase II and phase III to fight the cytokine release syndrome as a host-directed therapy.^{14,15} Hence, the maintenance therapy with CNIs might play a protective role in transplanted patients. In this cohort, we did not have patients with history of

transplantation of less than 2 years, as was the case with the Italian series.¹⁶ The low rate of admission in transplant recipients specially in the first years of transplantation might be due to protective effects of immunosuppressive agents against cytokine storm or modification of immunity function.

However, most centers including ours² stop the antimetabolite and significantly reduce the CNi level or even stop it, and keep the steroids, which was based on a low level of evidence. Despite discontinuation of CNi and antimetabolites in severe and hypoxemic cases and early initiation of antiviral treatment upon admission and treatment with IVIG (1-2 g/kg), the mortality rate was 45% in our center. This high mortality rate could be due to more severe disease among this population as noted in series of 20 patients in Italy,¹⁶ or delay in hospital referral with the mean time from onset of symptoms to admission which was 4.21 ± 3.7 days, and lack of effective antiviral agent. Lopinavir/ritonavir and ribavirin were given to all severe cases. Of note, based on a recent study, lopinavir/ritonavir has no benefit over standard of care.¹⁷ This might be one of the reasons of high mortality, as we still do not have a proven antiviral therapy.

Based on these findings and previously mentioned studies, there is a dilemma between timely discontinuation of immunosuppressive therapy and initiation of them as a host-directed therapy. It seems that early referral and commencement of effective antiviral treatment and legitimate management of immunosuppressive therapy may help to improve the survival.

As evidenced by lymphopenia and increasing evidence of reduced number and impaired function of T cells and NK cells¹⁸ on one hand, and substantial rise in pro-inflammatory cytokines on the other hand, we suggest evaluation of T cells and their subtype counts by flow cytometry, measurement of cytokines such as IL-6, IL-1 β , IL-17, D-dimer, ferritin and fibrinogen as a guide to early targeted treatment in order to reduce mortality. This might be of special importance among patients with diabetes, history of recent anti-rejection treatment, bilateral lung involvement in CT scan, positive d-dimer or troponin, and severe initial presentations.

Although transplant recipients seem to be affected less with severe type of disease (only 19 patients out of about 2500), which might be due to some levels of immunosuppression, patients who had a history of acute rejection and recent immunosuppressive intensification had worse outcomes.

One of the major limitations of our study was the small sample size. A larger cohort in a multicenter study may help to drive a more solid conclusion.

In conclusion, COVID-19 is a mysterious disease that presented as an infectious disease and evolved to a state of immunologic disturbances. Thereby, management of COVID-19 is a state of art, with initiation of antiviral therapy in early steps and thoughtful usage of immunosuppressive drugs.

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CONFLICT OF INTEREST

Authors disclose no conflict of interest.

AUTHOR CONTRIBUTIONS

S.S designed study conception. M.G performed data collection and carried out this work. M.N supervised the findings and helped in drafting manuscript. A.K verified the analytical methods and data analysis. S.S wrote the manuscript and N.D contributed in critical revision. A.A and A.F helped in analysis and interpretation of data. F.P and F.S involved in data collection. S.Z and S.F contributed to sample preparation.

The author(s) read and approved the final manuscript. All authors discussed the results and contributed to the final manuscript.

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