Original Article

Clinical Course and Outcomes of COVID-19 in Kidney Transplant Recipients

Divya Bajpai, Satarupa Deb, Sreyashi Bose, Chintan P. Gandhi, Tulsi Modi, Abhinav Katyal, Nikhil Saxena, Ankita Patil, Sunil Patil, Sayali Thakare, Atim Pajai, Ashwathy Haridas[1], Vaibhav S. Keskar[2], Sunil Y. Jawale[3], Amar G. Sultan[4], Gita Nataraj[5], Nayana Ingole[5], Tukaram E. Jamale

Departments of Nephrology and [5]Microbiology, Seth G. S. M. C. and K. E. M. Hospital, Mumbai, Maharashtra, [1]Department of Nephrology, Apollo Hospital, Navi Mumbai, Maharashtra, [2]Kimaya Kidney Care, Thane, Maharashtra, [3]Yashwant Kidney Care, Pune, Maharashtra, [4]Amardeep Kidney Care, Akola, Maharashtra, India

Received: 19-11-2020
Revised: 29-12-2020
Accepted: 15-09-2021
Published: 17-06-2022

Address for correspondence:
Dr. Divya Bajpai, Department of Nephrology, Ward No. 34a, Third Floor, Seth G. S. M. C. and K. E. M. Hospital, Parel, Mumbai – 400012, Maharashtra, India.
E-mail: divyaa24@gmail.com

Access this article online

Website: www.indianjnephrol.org

DOI: 10.4103/ijn.IJN_509_20

Quick Response Code:

Abstract

Introduction: Kidney transplant recipients (KTR) are at increased risk of morbidity and mortality due to coronavirus disease 2019 (COVID-19). This study aimed to explore the clinical characteristics and outcomes of COVID-19 in KTR. **Methods:** We reviewed the clinical profile, outcomes, and immunological responses of recipients admitted with COVID-19. We determined the risk factors for mortality and severe COVID-19. **Results:** Out of 452 recipients on follow-up, 60 were admitted with COVID-19. Prevalent comorbidities were hypertension (71%), diabetes (40%), lung disease (17%). About 27% had tuberculosis. The median Sequential Organ Failure Assessment score at presentation was 3 (interquartile range [IQR] 1–5). There was a high incidence of diarrhea (52%) and anemia (82%). Treatment strategies included antimetabolite withdrawal (85%), calcineurin inhibitor decrease or withdrawal (64%), increased steroids (53%), hydroxychloroquine (21%), remdesivir (28.3%), and tocilizumab (3.3%). Severe COVID-19 occurred in 34 (56.4%) patients. During a median follow-up of 42.5 days (IQR 21–81 days), 83% developed acute kidney injury (AKI) and eight (13%) died. Mortality was associated with the baseline graft dysfunction, hypoxia at admission, lower hemoglobin and platelets, higher transaminases, higher C reactive protein, diffuse radiological lung involvement, hypotension requiring inotropes, and Kidney Diseases Improving Global Outcomes (KDIGO) stage 3 AKI (univariate analysis). Around 57% of patients remained RT-PCR positive at the time of discharge. By the last follow-up, 66.6% of patients developed IgM (immunoglobulin M) antibodies and 82.3% of patients developed IgG antibodies. **Conclusion:** COVID-19 in kidney transplant recipients is associated with a high risk of AKI and significant mortality.

Keywords: *COVID-19, kidney transplantation, mortality, outcomes, predictors*

Introduction

Chronic immunosuppression, comorbidities, and frequent exposure to health care facilities make kidney transplant recipients (KTR) especially vulnerable to respiratory viral illnesses,[1] including coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[2] Historically, transplant recipients are known to have an increased risk of severe viral pneumonia leading to acute respiratory distress syndrome[3,4] and are also at risk of developing subsequent fungal and bacterial infections.[5] SARS-CoV-2 primarily affects the respiratory tract, but it is also associated with cytokine release syndrome leading to multiorgan dysfunction.[6] The nature of the immune response against SARS-CoV-2 in KTR who have diminished T-cell immunity remains unknown. It is hypothesized that chronic immunosuppression may abrogate the proinflammatory response in COVID-19, which is associated with mortality.[7,8] However, there is evidence suggesting higher mortality due to COVID-19 in KTR.[9] Also, there are early reports of a high incidence of AKI.[8] Similar evidence from developing countries is lacking. This population poses unique challenges in terms of risk assessment, interpretation of inflammatory markers, management of immunosuppression, and preservation of kidney allograft function.

As the COVID-19 pandemic is rapidly intensifying, there is an urgent need to expand our understanding of COVID-19 in KTR to guide management strategies. We present a comprehensive evaluation of the epidemiology, clinical presentation, management, and outcomes of COVID-19 in KTR from western Maharashtra, which is the epicenter of COVID-19 in India.

How to cite this article: Bajpai D, Deb S, Bose S, Gandhi CP, Modi T, Katyal A, *et al.* Clinical course and outcomes of COVID-19 in kidney transplant recipients. Indian J Nephrol 2022;32:467-75.

Materials and Methods

Study design and participants

Out of 452 KTR following up at four tertiary referral centers in western Maharashtra, all adults (>18 years) diagnosed with COVID-19 between March 2020, and September 2020 (6 months) were included in this cohort study. Patients with a presumed and suspected diagnosis were excluded. The study was approved by the institutional ethics committee (EC/OA-112/2020) with a waiver of consent. It was registered with the Clinical Trials Registry, India (CTRI/2020/06/026000). The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Data collection

We obtained data on demographics, comorbidities, past medical history, concomitant medication use, clinical presentation, hospital course, laboratory parameters, treatment, and outcomes. All the patients were admitted to the renal high-dependency unit managed by nephrologists. Five critically ill patients were shifted to the intensive care unit. Outcomes were recorded at the time of discharge from the hospital/death, and at the time of the subsequent follow-up visit in the transplant clinic after discharge. Post-discharge follow-up was available for 100% of the patients.

Laboratory procedures

SARS-CoV-2 infection was diagnosed in nasopharyngeal swabs by reverse transcription–polymerase chain reaction (RT-PCR), which were repeated every 5 days till they are confirmed negative or the discharge of the patients from the hospital. The immunological response was assessed by testing anti-COVID-19 antibodies. Initially (till June 2020), the antibody kit used was "STANDARD Q COVID-19 IgM/IgG Duo," which is manufactured by SD Biosensor, which is used for the qualitative detection of specific immunoglobulin M (IgM) and IgG to COVID-19. Subsequently, "COVID Kavach ELISA" was used. It is manufactured by the National Institute of Virology, Pune, and the Indian Council of Medical Research. This kit targets whole-cell antigen instead of nucleocapsid or spike protein antigen and thus has broader sensitivity. Laboratory investigations included complete blood count, kidney and liver function tests, coagulation profile (D-Dimer). Assessment for lactate dehydrogenase (LDH), serum ferritin, C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin, and troponin I was performed at the discretion of the treating physician. The Sequential Organ Failure Assessment (SOFA) score[10] was calculated at the time of admission to the hospital.

Clinical outcome assessment and definitions

The primary outcome was mortality. The secondary outcome was the development of severe COVID-19, which was defined as oxygen saturation (SpO_2) ≤94% at room air or acute respiratory distress syndrome [Partial pressure of oxygen (P_aO_2)/fraction of inspired oxygen (F_iO_2) <300]. Baseline graft function was assessed by estimated glomerular filtration rate (eGFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. Acute kidney injury (AKI) was classified as per the Kidney Diseases Improving Global Outcomes (KDIGO) staging. The SOFA score was used to the assess the severity of organ dysfunctions.[11] Anemia was defined at hemoglobin <12 g/dL. Tacrolimus trough levels more than 7 ng/mL after first-year posttransplant were considered supratherapeutic.

Statistical analysis

We presented categorical variables as counts and percentages. We calculated the mean and standard deviation for continuous variables, which were normally distributed (Shapiro test), and median and interquartile range (IQR) for those that were not. For comparison of categorical variables, we used Fisher's exact test when observations were less than 5, and Chi-square test when they were not. For continuous variables that were normally distributed, we used *t*-test, and for not-normally distributed data, we used Mann–Whitney *U* test. We used logistic regression for multivariate analysis. The significance level was fixed at $P < 0.05$, and all tests were two-tailed.

Results

Patient characteristics

From March 2020, to September 2020, out of 452 KTR on follow-up, 60 were admitted with a diagnosis of COVID-19. Fifty-nine patients had a positive RT-PCR for SARS-CoV-2, one patient had positive immunoglobulin M (IgM) antibody against SARS-CoV-2 with clinical signs and symptoms. The median follow-up was 42.5 days (IQR 21–81 days). Forty-nine (81.7%) patients were male, and the mean age was 44 (± 11) years [Table 1]. The most common comorbidity was hypertension (71%), followed by diabetes (40%). The median duration from transplant to the diagnosis of COVID-19 was 5.37 years (IQR 27–87 months). Seven patients got infected in the first year after transplant. Thirty-one (51.2%) patients had received antibody induction at the time of transplant, 100% patients were on steroids as maintenance immunosuppression, and 93% were on both calcineurin inhibitor and an antimetabolite. The mean eGFR at baseline was 57.90 (± 20.4) mL/minute/1.73 m^2, 20 (33%) patients had a history of allograft rejection in the past and were treated for the same, and 17 (28%) had proteinuria at baseline.

Table 1: Baseline demographics and medication use

Variable	Total (*n*=60)	Severe COVID-19 (*n*=34)	Mild/Moderate COVID-19 (*n*=26)	*P*
Age (years)	44.23±11.08	44.32±11.71	41.88±10.86	0.413
Male	49 (81.7%)	28 (82.4%)	21 (80.3%)	0.999
Time since transplant to SARS-CoV-2 positivity (months)	64.5 [27-87]	61.5 [22-87]	66 [35-96.5]	0.794
Days from SARS-CoV-2 positivity until last follow-up or death	42.5 [21-81]	36 [12-70]	45 [21.5-91]	—
Comorbidities				
Diabetes mellitus (pre- or posttransplant)	24 (40%)	14 (41.2%)	10 (38.5%)	0.834
Hypertension	43 (71.1%)	28 (82.2%)	15 (57.7%)	0.036
Heart disease	4 (6.7%)	3 (8.8%)	1 (3.8%)	0.626
Lung disease	10 (16.7%)	5 (14.6%)	5 (19.2%)	0.733
Tuberculosis (active or historical)	16 (26.7%)	8 (23.5%)	8 (30.8%)	0.531
Smoker	4 (6.7%)	2 (5.9%)	2 (7.7%)	0.999
Type of transplant (LRDT vs. DDT)	51 (85%)	29 (85.4%)	22 (84.6%)	1
Kidney from marginal donors*	4/53 (7.5%)	1/27 (3.7%)	3/26 (11.5%)	0.352
Etiology of kidney disease				
Diabetes	3 (5.0%)	2 (5.9%)	1 (3.8%)	
Glomerular	8 (13.3%)	4 (11.7%)	4 (15.3%)	
Polycystic kidney disease	2 (3.3%)	1 (2.9%)	1 (3.8%)	—
CAKUT	8 (13.3%)	5 (14.7%)	3 (11.5%)	
Unknown	37 (61.6%)	22 (64.7%)	15 (57.7%)	
Others	2 (3.3%)	0	2 (7.7%)	
BMI (kg/m^2)	24.73±5.27	24.51±4.59	25.01±6.07	0.719
Medications				
Antibody induction (antithymocyte globulin/basiliximab/grafalon)	31 (52.5%)	18 (54.5%)	13 (50%)	0.796
Calcineurin inhibitor	56 (93.3%)	33 (97.1%)	23 (88.5%)	0.307
Mycophenolate mofetil	47 (78.3%)	25 (73.5%)	22 (84.6%)	0.302
Azathioprine	8 (13.3%)	5 (14.7%)	3 (11.5%)	0.719
mTOR inhibitor	3 (5.0%)	2 (5.8%)	1 (3.8%)	1
Steroids	60 (100%)	34 (100%)	26 (100%)	—
ACEi/ARB	10 (16.7%)	3 (8.8%)	7 (26.9%)	0.085
Baseline eGFR (CKD-EPI mL/minute/1.73 m^2)	57.90±20.43	55.47±20.08	61.08±19.75	0.296
Baseline proteinuria (>500 mg/day)	17 (28.3%)	14 (41.2%)	3 (11.5%)	0.012
Historical allograft rejection	20 (33.3%)	15 (44.1%)	5 (19.5%)	0.043
Blood group				
O+	18/51 (35.3%)	10/27 (37.2%)	8/24 (33.3%)	0.826
A+	10/51 (19.6%)	4/27 (14.8%)	6/24 (25%)	
B+	21/51 (41.2%)	12/27 (44.4%)	9/24 (37.4%)	
AB+	2/51 (3.9%)	1/27 (3.7%)	1/24 (4.2%)	

COVID-19 - coronavirus disease 2019; SARS-CoV-2 - severe acute respiratory syndrome coronavirus-2; CAKUT - congenital anomaly of kidney and urinary tract; BMI - body mass index; LRDT - Living-related donor transplant; DDT - deceased donor transplant; mTOR - mechanistic target of rapamycin; ACEi - angiotensin-converting enzyme inhibitor; ARB - angiotensin II receptor blockers; eGFR - estimated glomerular filtration rate; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration. *Data were not available for marginal donors (*n*=7), blood group (*n*=9)

Clinical presentation and outcomes

Fever was the most common presenting complaint (90%) followed by fatigue (75%) [Table 2 and Supplementary Table 1]. Thirty-one patients (52%) had diarrhea at the time of presentation, and it was an isolated manifestation in four patients. Orthostatic hypotension was present in 17 (28.3%) patients. Eight (13.3%) patients had hypotension requiring inotropic support. The median SOFA score at admission was 3 (IQR = 1–5, range 0–11). Forty-nine (81.7%) patients had anemia and 47 (78.3%) patients had a drop (≥1 mg/dL) in their hemoglobin value from the baseline. The mean drop in hemoglobin from baseline was 2.05 (± 1.29) g/dL. Six (10%) patients had active bleeding during the hospital

Table 2: Clinical presentation and laboratory parameters

Variable	Total (*n*=60)	Severe COVID-19 (*n*=34)	Mild/Moderate COVID-19 (*n*=26)	*P*
Parameters at admission				
Fever	54 (90%)	33 (97%)	21 (80.8%)	0.076
Dyspnea	36 (60%)	31 (91.2%)	5 (19.2%)	<0.001
Diarrhea	31 (51.7%)	19 (55.9%)	12 (46.2%)	0.455
Systolic BP	122.17±22.06	124.47±25.88	119.16±15.85	0.347
Diastolic BP	75.45±16.19	76.06±18.10	74.58±13.6	0.734
Pulse	104.2±15.52	106.1±15.29	101.69±15.82	0.266
Respiratory rate	20 [18-27]	22.5 [20-31]	18 [16-20]	<0.001
Presence of orthostatic hypotension*	17/48 (35.4%)	9/26 (34.6%)	8/22 (36.3%)	0.714
SOFA Score on admission Median [IQR]	3 [1-5]	4 [2.75-6]	1.5 [1-3]	<0.001
Hemoglobin (g/dL)	11.27±2.39	10.58±2.46	12.15±2.09	0.012
White blood cell count (× 10^9/L)	5.76 [3.40-7.00]	4.70 [3.18-6.74]	5.91 [4.22-7.24]	0.177
Lymphocyte count (per µL)	8.60 [4.85-12.90]	9.00 [4.85-13.00]	6.94 [4.95-12.00]	0.475
Platelet count (× 10^9/L)	1.5 [1.10-2.21]	1.40 [1.11-2.53]	1.62 [1.08-2.05]	0.897
Serum creatinine (mg/dL)	2.1 [1.4-3.3]	2.32 [1.4-4.24]	1.67 [1.44-2.48]	0.160
SpO_2 at admission	97 [94-98]	95 [90-98]	98 [97-98]	0.003
Worst parameters during the course of illness				
Hemoglobin (g/dL)	9.91±2.52	9.11±2.67	10.90±1.95	0.006
Drop in hemoglobin from baseline (g/dL)	2.05±1.29	2.34±1.42	1.69±1.01	0.05
White blood count (per µL)	4.10 [2.77-5.61]	3.30 [2.03-5.94]	4.35 [3.20-4.95]	0.260
Lymphocyte count (per µL)	6.84 [3.68-11.20]	8.05 [3.50-12.60]	6.35 [3.68-9.65]	0.487
Platelet count (× 10^9/L)	1.35 [1.00-1.70]	1.30 [0.75-1.60]	1.35 [1.05-1.85]	0.259
Blood urea nitrogen (mg/dL)	31 [22-50.75]	47.5 [28.75-78.5]	24.5 [19-34.75]	<0.001
Serum creatinine (mg/dL)	2.40 [1.70-4.70]	3.00 [1.80-6.00]	1.98 [1.67-2.65]	0.022
Serum bicarbonate (mEq/L)	14 [11.8-18.5]	13.0 [11-17]	16.0 [13.25-19]	<0.037
Serum sodium (mEq/L)	129 [126-133]	129 [124-133]	129 [126-131]	0.655
Serum potassium (mEq/L)	3.90 [3.450-4.54]	3.95 [3.42-4.92]	3.84 [3.45-4.45]	0.822
Aspartate transaminase (U/L)	37 [24-56]	44.5 [26.5-59.5]	27 [23.5-43.5]	0.176
Alanine transaminase (U/L)	26 [14.5-46.25]	29 [19-65]	18 [13-34]	0.079
Diffuse (>50%) lung involvement on imaging	22 (36.7%)	22 (64.7%)	0	<0.001
C-reactive protein (mg/L)	51.0 [23.6-97]	86.75 [38-155]	26 [14-57.1]	0.002
Lactate dehydrogenase, U/L	685 [433-1123]	855 [499-1375]	487 [409.5-691]	0.025
D-Dimer (µg/ml)*	0.89 [0.54-2.17]	0.75 [0.41-2.24]	1.18 [0.79-1.78]	0.349
Serum ferritin (µg/L)	898 [400-1209]	910 [467-1246]	800 [346-1059]	0.494
IL-6 (pg/mL)	19.8 [8.91-189]	25.95 [9.50-331.75]	25.35 [7.12-120.3]	0.456
Presence of supratherapeutic tacrolimus trough levels (C_0)	13 (21.67%)	7 (20.58%)	6 (23.07%)	0.995
Median C_0 level [IQR]	5.92 [3.21-8.07]	—	—	—

COVID-19 - coronavirus disease 2019; BP - blood pressure; SOFA - sequential organ failure assessment; SpO_2 - oxygen saturation; IL - interleukin; IQR - interquartile range *Data missing for orthostatic hypotension (*n*=12); lung involvement (*n*=1); D-Dimer (*n*=40); C-reactive protein (*n*=17); lactate dehydrogenase (*n*=21); serum ferritin (*n*=42); interleukin-6 (*n*=45); tacrolimus trough levels C_0 (*n*=25)

course (one patient had nasal bleeding, one hemoptysis, three malena, and one menorrhagia). Four (6.67%) patients required blood transfusion for symptomatic anemia. Thirty-seven (61.67%) patients had leukopenia and 41 (68.3%) had lymphopenia. Elevated transaminases were seen in 29 (48.3%) patients and two (3.3%) had elevated bilirubin. Inflammatory markers were elevated in most of the patients [Table 2].

Twenty-two (36.67%) patients had diffuse (>50%) involvement on imaging (chest X-ray or computed tomography [CT]). CT scan was available for 38 patients, and the most common finding was peripheral multifocal ground-glass opacities seen in 86.8% of patients. Other features seen were reticular opacities (42%), patchy consolidations (18.4%), interlobular septal thickening (24%), adjacent pleural thickening (10.5%), and sub-centimeter-sized mediastinal lymphadenopathy (52.6%). About 21% had fibrosis. Five patients had evidence of pulmonary tuberculosis on CT scan. A semiquantitative CT severity scoring, proposed by Pan *et al*.[12] was available for 26 patients with a median [IQR] of 9 [5, 11.5]. Thirty-three patients (55%) had tachycardia (heart rate >100/minute). Electrocardiogram was available

for 26 (43.4%) patients. Abnormalities seen were PR prolongation (seven patients), prolonged QTc (three patients), atrial ectopics (two patients), localized T inversion (four patients), ST depression (four patients), ST elevation (two patients). Troponin-I was elevated in six out of 11 patients.

Out of 35 patients in whom tacrolimus trough levels (C_0) were checked, 13/35 (37%) had supratherapeutic levels. Nine out of 13 patients had diarrhea. Ten out of 13 patients were poor tacrolimus metabolizers (CYP3A5 [Cytochrome P450 Family 3 Subfamily A Member 4] *3/*3 alleles). Dose-adjusted levels were calculated for these patients to compare with historical trough levels. In 11 out of 13 patients, dose-adjusted C_o levels showed an increase after COVID-19 [Supplementary Table 2].

Severe COVID-19

Thirty-four (56.41%) patients developed severe COVID-19. Of these, 16 out of 34 had hypoxia at presentation and 18 patients developed hypoxia during the ward course. Eleven (18.33%) patients required assisted ventilation by either noninvasive positive pressure ventilation (NIPPV) or intubation. Eight (13.34%) patients with severe COVID-19 died [Table 3]. Hypertension and history of allograft rejection episodes, and proteinuria at baseline were significantly associated with severe COVID-19 [Table 1]. Patients with severe COVID-19 had a higher SOFA score on admission (median 4 vs. 1.5), lower hemoglobin, and a higher drop in hemoglobin from baseline. They had higher levels of CRP, LDH, blood urea nitrogen, serum creatinine, and lower serum bicarbonate. They were more likely to have diffuse lung involvement of imaging, hypotension requiring inotropes, and KDIGO Stage 3 AKI [Table 2]. In multivariate regression analysis, severe anemia (hemoglobin <9 g/dL; P = 0.021), adjusted odds ratio (aOR) 16.9 (95% confidence interval [CI] 1.54, 187.5), high SOFA score on admission (P = 0.002, aOR 2.39, 95% CI 1.39, 4.11), and decreased baseline eGFR (P = 0.044, aOR 0.054, 95% CI 0.003, 0.93) significantly predicted severe COVID-19 [Table 4].

COVID-19 and graft function

Fifty (83.3%) patients had AKI of which 17 (28.3%) had Stage 3 AKI according to KDIGO staging [Table 3]. Nine (15%) patients were dialyzed during the hospital course and three patients remained at dialysis till the last follow-up (>2 months), and the remaining six patients died. Two patients were readmitted after 10 days with acute graft dysfunction and required hemodialysis. Graft biopsy showed chronic active antibody-mediated rejection in the first patient, and he remains on maintenance dialysis despite treatment with intravenous immunoglobulin. The second patient has transplant glomerulopathy in the biopsy and his eGFR remains below 15 mL/min/1.73 m^2.

Table 3: Management strategies and clinical outcomes

Variable	Total (n=60)	Severe COVID-19 (n=34)	Mild/Moderate COVID-19 (n=26)	P
MMF/AZA withdrawal*	47/55 (85.45%)	29/30 (96.67%)	18/25 (72%)	0.018
CNI withdrawal or decrease[#]	36/56 (64.3%)	23/33 (69.7%)	13/23 (56.5%)	0.398
Increased steroids	32 (53.3%)	27 (79.4%)	5 (19.2%)	<0.001
Antibiotics	49 (81.7%)	30 (88.2%)	19 (73.1%)	0.182
Hydroxychloroquine	13 (21.7%)	9 (26.5%)	4 (15.4%)	0.359
Remdesivir	17 (28.3%)	14 (41.2%)	3 (11.5%)	0.012
Tocilizumab	2 (3.34%)	2 (5.88%)	0	0.999
Azithromycin	31 (51.7%)	21 (61.8%)	10 (38.5%)	0.073
Heparin	37 (61.7%)	28 (82.4%)	9 (34.6%)	<0.001
Total days of hospitalization	12 [9-18]	13 [10-20.5]	11.5 [8.5-15.5]	0.170
Days of oxygen supplementation	3 [0-6]	5 [3.5-8.0]	0	<0.001
Highest level of oxygen support required				
Nasal prongs/face mask/nonrebreathing mask	21 (35%)	21 (61.8%)	0	—
NIPPV/High-flow nasal oxygen	3 (5%)	3 (8.8%)	0	
Intubation	8 (13.3%)	8 (23.5%)	0	
Inotropes requirement Hypotension	8 (13.3%)	8 (23.5%)	0	0.030
Acute graft injury [KDIGO Stage 3]	17 (28.3%)	16 (47.1%)	1 (3.8%)	<0.001
Hemodialysis	9 (15%)	9 (26.5%)	0	0.004
Death	8 (13.3%)	8 (23.5%)	0	0.008
Readmission	2 (3.34%)	2 (5.88%)	0	—
On hemodialysis >1 months	4 (6.67%)	4 (11.76%)	0	0.095

COVID-19 - coronavirus disease 2019; MMF - mycophenolate mofetil, AZA - azathioprine, CNI - calcineurin inhibitor; NIPPV - noninvasive positive pressure ventilation KDIGO - kidney diseases improving global outcomes. *Not on antimetabolite: n=5; Decreased AZA but not stopped for n=1; [#] Not on CNI: n=4

Presence of coinfections

During the course of illness, two patients developed pyelonephritis (*E. coli* and *Pseudomonas*). One patient developed ileocecal intussusception and septicemia with acinetobacter. One patient was readmitted with hemoptysis and found to have lobar consolidation. Sputum studies and respiratory multiplex PCR (BioFire FilmArray) were negative. All these patients responded to appropriate antibiotics.

Immunosuppression modulation and treatment of COVID-19

All patients with severe COVID-19 were treated with either intravenous dexamethasone 6 mg or methylprednisolone 40 mg for a period of 7 or 10 days as per the clinical condition. In patients with the non-severe disease, the steroid dose was maintained the same. Antimetabolite was stopped in 47/55 (85.45%) patients, and it was decreased in two patients. Calcineurin inhibitors (CNI) were either stopped or decreased in 36/56 (64.3%) patients. Remdesivir was given to 17 (28.3%) patients with severe COVID-19. The dose administered was 600 mg over 5 days for 16 patients and one patient received 1,100 mg over 10 days. None of the patients developed any worsening of kidney or liver functions following remdesivir. On recovery, the steroid was tapered to the original dose, and antimetabolite was reintroduced at reduced doses in the first week after discharge. Calcineurin inhibitor dosages were guided by trough concentrations.

Risk factors associated with mortality

Over a median follow-up of 42.5 days (IQR 21–81 days), there were eight (13.3%) deaths. Demographic, clinical, and laboratory parameters that were significantly different between survivors and non-survivors are listed in Table 5. Non-survivors were more likely to have diabetes mellitus, proteinuria at baseline (75% vs. 21%), history of allograft rejection (87% vs. 25%), and lower baseline eGFR. On univariate analysis, they had lower SpO_2 at admission, lower hemoglobin and platelet count, higher SOFA score at admission, higher transaminases, and higher CRP were more likely to have diffuse radiological lung involvement, hypotension requiring inotropes, and AKI requiring hemodialysis [Table 5]. In multivariate regression analysis, a combination of hypotension requiring inotropes and AKI [KDIGO Stage 3] led to significant improvement in the model prediction of mortality (86%–98%) [Table 4], but they did not independently predict mortality.

Time to RT-PCR negativity and development of anti-COVID-19 antibodies

Repeat RT-PCR was available at the time of discharge/death for 35 patients. It remained positive in 20/35 (57%) patients. For two of these patients, RT-PCR remained positive till the end of 4 weeks.

Anti-COVID-19 IgM antibodies were available for 15 patients. Ten (66.6%) patients achieved positive IgM antibodies. IgG antibodies were available for 34 patients. IgG antibodies were repeated weekly till they turned positive. Seventeen (50%) patients had positive IgG antibodies at 2 weeks. Subsequently, IgG positivity was attained by five (14.7%) patients at 3 weeks, five (14.7%) at 4 weeks, and one (4.3%) at 6 weeks. Three (8.8%) patients did not achieve positive IgG antibodies even at the end of 12 weeks, one (4.3%) patient is negative at 4 weeks, and two (5.8%) patients are negative for IgG at 3 weeks at present [Supplementary Table 3].

Discussion

We report 60 KTR diagnosed with COVID-19, of which 34 (57%) had severe disease and eight (13%) died. A high incidence of AKI (83%) was noted with 15% of patients requiring dialysis. Among the clinical features, we noted a high incidence of diarrhea (52%) and anemia (82%). Patients with severe COVID-19 were treated with increased corticosteroids, and 17 (28%) patients received remdesivir.

Our data demonstrate a lower mortality rate of 13% as compared with prior reports by single centers [13-15] or by international registries,[16] which have reported mortality rates of 24% to 32% in hospitalized transplant recipients. This lower mortality can be attributed to younger age (44 ± 11 years) and lower comorbidities in our patients as compared with those previously reported. Also, as per practice pattern, all our recipients are on regular telephonic follow-up with the nephrologists and reported immediately to the transplant unit at the onset of any complaints, which might have led to the early diagnosis. Lower mortality can also be due to differences in SARS-CoV-2 strains or genetic susceptibility.

Interestingly, diarrhea was a presenting feature in 52% of patients, which is higher than that previously reported in transplant recipients (22%–38%)[14,16] and in the general population (3%–24%).[17,18] Four of these patients lacked respiratory symptoms at presentation. Angiotensin-converting enzyme 2 receptors are widely expressed in the gastrointestinal tract, which might explain in part the tropism of SARS-CoV-2 to the gut.[19,20] Transplant recipients are at high risk for diarrhea secondary to infections or due to immunosuppressive drugs. Our data suggest that it is important to suspect and test for COVID-19 in kidney transplant recipients presenting with diarrhea without respiratory symptoms.

About 82% of patients had anemia and 78% had ≥1 g/dL drop (range 0–5 g/dL) in their hemoglobin from baseline with four patients requiring blood transfusion. Six of our patients had active bleeding, which contributed to anemia. Anemia was a significant predictor of severe COVID-19 in our study. This is in concordance with a meta-analysis suggesting an association of anemia with severe COVID-19.[21]

Table 4: Regression analysis results

	B	SE	df	Significance	Exp (*B*)	95% CI for Exp (*B*)	
						Lower	Upper
Model for prediction of severe COVID-19							
Decreased baseline eGFR	−2.918	1.448	1	0.044	0.054	0.003	0.924
Severe anemia (hb <9 g/dL)	2.833	1.225	1	0.021	16.999	1.541	187.525
SOFA score on admission	0.873	0.277	1	0.002	2.394	1.392	4.119
Constant	−2.705	0.844	1	0.001	0.067		
Model for prediction of death due to COVID-19							
	−21.077	4.755E3	1	0.998	0.000	0.000	—
	−36.001	7.062E3	1	0.997	0.000	0.000	—
	18.880	4.755E3	1	0.996	1.583E8		-

SE - standard error; df - degrees of freedom; CI - confidence interval; COVID-19 - coronavirus disease 2019; eGFR=estimated glomerular filtration rate; hb - hemoglobin; SOFA - Sequential Organ Failure Assessment

Table 5: Demographic, clinical, and management parameters that are significantly different in survivors and non-survivors

Variable	Total (*n*=60)	Survivors (*n*=52)	Non-survivors (*n*=8)	*P*
Baseline characteristics				
Baseline eGFR (CKD-EPI mL/minute/1.73 m^2)	57.90±20.43	60.12±20.10	48.38±17.40	0.031
Baseline proteinuria (>500 mg/day)	17 (28.3%)	11 (21%)	6 (75%)	0.015
Historical allograft rejection	20 (33.3%)	13 (25.0%)	7 (87.5%)	0.001
At admission				
Dyspnea	36 (60%)	28 (53.8%)	8 (100%)	0.017
SpO_2	97 [94-98]	97.5 [95.25-98]	88 [79.5-96]	0.030
Hemoglobin (g/dL)	11.27±2.39	11.60±2.27	9.11±2.04	0.005
Platelet count (× 10^9/L)	1.5 [1.10-2.21]	1.40 [1.06-1.92]	0.80 [0.56-0.99]	0.028
Serum creatinine (mg/dL)	2.1 [1.4-3.3]	1.80 [1.4-2.78]	4.07 [1.77-7.82]	0.051
SOFA Score Median [IQR]	3 [1-5]	3 [1-4]	6 [5-8]	<0.001
Worst parameters during the course of illness				
Hemoglobin (g/dL)	9.91±2.52	10.2±2.44	7.52±1.68	0.003
Platelet count (× 10^9/L)	1.35 [1.00-1.70]	1.40 [1.07-1.87]	0.70 [0.57-0.95]	0.001
Blood urea nitrogen (mg/dL)	31 [22-50.75]	30 [21-42]	59 [79-109]	<0.001
Serum creatinine (mg/dL)	2.40 [1.70-4.70]	2.30 [1.60-2.90]	5.90 [4.75-6.25]	0.001
Serum bicarbonate (mEq/L)	14 [11.8-18.5]	16 [12.25-19]	11 [8.70-13]	0.005
Aspartate transaminase (U/L)	37 [24-56]	28 [23-53]	61.5 [47.5-493.75]	0.001
Alanine transaminase (U/L)	26 [14.5-46.25]	23.5 [14-31.75]	76.5 [65.5-291]	<0.001
C-reactive protein (mg/L)	64.0 [31-105]	51 [27-81.5]	234.4 [178-238]	<0.001
Diffuse (>50%) lung involvement on imaging	22 (36.7%)	14 (27.5%)	8 (100%)	<0.001
Inotropes requirement Hypotension	8 (13.3%)	1 (1.9%)	7 (87.5%)	<0.001
Acute graft injury [KDIGO Stage 3]	17 (28.3%)	9 (17.35%)	8 (100%)	<0.001
Hemodialysis	9 (15%)	3 (5.88%)	6 (75%)	<0.001
Presence of severe COVID-19	34 (56.4%)	26 (50%)	8 (100%)	0.008

eGFR - estimated glomerular filtration rate; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration; SpO_2 - oxygen saturation; COVID-19 - coronavirus disease 2019; KDIGO - kidney diseases improving global outcomes; SOFA - Sequential Organ Failure Assessment; IQR - interquartile range

Proposed mechanisms for these associations include severe inflammatory response, denaturation of hemoglobin secondary to its interaction with SARS-CoV-2, and iron metabolism dysregulation leading to oxidative stress.[22] This has implications in the early detection and prompt management of patients with impending complications.

Eighteen out of 34 patients who developed severe disease had no hypoxia at presentation and worsened during hospital course. Two patients who succumbed did not have hypoxia at presentation. This underscores the importance of close monitoring of respiratory signs in kidney transplant recipients who present with mild disease at presentation. Also, there is a need to identify markers of severe disease that might precede the development of respiratory distress (e.g., anemia). Patients with mild symptoms who are planned for outpatient care

should be monitoring their oxygen saturation levels at home, which can be communicated to the physician via teleconferencing.

Among the various baseline characteristics evaluated, decreased eGFR, proteinuria, and a history of treatment for graft rejection were associated with severe COVID-19 and mortality. This may be due to the cumulative increase in the level of immunosuppression due to antirejection therapy, making them vulnerable to severe disease. However, as the role of immune response in COVID-19 is complex, this is hypothesis generating and warrants further evaluation.

About 83% of our patients had AKI, 28% were classified as KDIGO Stage 3, and 15% required hemodialysis. Four patients remained on maintenance hemodialysis. This is significantly higher compared with earlier studies that reported a lower incidence of acute graft dysfunction from 13.3% to 52%.[13,16,23] The presence of diarrhea, supratherapeutic tacrolimus levels, and severe hypotension might have contributed to higher rates of AKI in our patients. Whether high tacrolimus levels are due to diarrhea or the direct toxicity of SARS-CoV-2 to the gastrointestinal tract needs further evaluation. Multiple factors have been suggested to contribute to AKI in patients with COVID-19, including impaired kidney perfusion, inflammatory syndrome–mediated injury, or direct toxicity of SARS-CoV-2.[24,25] Our data suggest an association of KDIGO Stage 3 AKI with severe COVID-19 and mortality. Thus, the graft function should be closely monitored and patients with AKI should be considered vulnerable for the development of complications.

To date, there is no proven therapy for COVID-19. We gave remdesivir to 17 patients with severe disease, and it was well tolerated. Due to the small number of patients, it is difficult to comment about the efficacy, but our data point toward the safety of remdesivir in kidney transplant recipients.

Repeat RT-PCR testing revealed that 57% of patients had positive RT-PCR at the time of discharge. Immunological response varied among the patients. IgM positivity rate was at 66.6%. Around 50% of patients had positive IgG antibodies at 2 weeks. Three patients did not achieve IgG positivity even by 12 weeks. In a study on the general population from Wuhan, Liu *et al.*[26] reported an IgM positivity rate of 60%, and 21.4% of cases did not have an IgG response. Furthermore, larger studies are needed to understand the immunological responses in transplant recipients.

Comprehensive evaluation and meticulous follow-up (range 3147 days) are the notable merits of this study. It was limited by a small sample and retrospective nature, and we hope that the findings of this exploratory study will form the basis of formal hypothesis driving larger studies in the future.

In conclusion, our data suggest that COVID-19 in KTR is associated with significant morbidity and high rates of AKI. Mortality due to COVID-19 in our patients was lower than previously reported. A combination of hypotension requiring inotropes and AKI (KDIGO Stage 3) led to significant improvement in the model prediction, but they did not independently predict mortality.

Acknowledgments

We thank our dean Dr Hemant Deshmukh for the permission and support for conduct of the study. We acknowledge the support of Dr. Pratap Jadhav (Professor, Department of Community Medicine, Seth G. S. M. C. and K. E. M. Hospital, Mumbai) in conducting statistical analysis for this study. We acknowledge the help of Dr. Bharat Jagiasi (Intensivist, Reliance Hospital, Navi Mumbai) for data collection at one of the centers.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cordero E, Perez-Romero P, Moreno A, Len O, Montejo M, Vidal E, *et al*. Pandemic influenza A (H1N1) virus infection in solid organ transplant recipients: Impact of viral and non-viral co-infection. Clin Microbiol Infect 2012;18:67-73.
2. Samavat S, Nafar M, Firozan A, Pourrezagholi F, Ahmadpoor P, Samadian F, *et al*. COVID-19 rapid guideline in kidney transplant recipients. Iran J Kidney Dis 2020;14:231-4.
3. Helanterä I, Anttila VJ, Lappalainen M, Lempinen M, Isoniemi H. Outbreak of influenza A (H1N1) in a kidney transplant unit—Protective effect of vaccination. Am J Transplant 2015;15:2470-4.
4. Joob B, Wiwanitkit V. Novel H1N1 influenza infection among post-renal transplantation subjects: A mini review. Saudi J Kidney Dis Transpl 2015;26:1006-8.
5. Manuel O, Estabrook M; American Society of Transplantation Infectious Diseases Community of Practice. RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13511. doi: 10.1111/ctr.13511.
6. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020;368:473-4.
7. Vishnevetsky A, Levy M. Rethinking high-risk groups in COVID-19. Mult Scler Relat Disord 2020;42:102139.
8. Molnar MZ, Bhalla A, Azhar A, Tsujita M, Talwar M, Balaraman V, *et al*. Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States. Am J Transplant 2020;20:3061-71.
9. Caillard S, Anglicheau D, Matignon M, Durrbach A, Greze C, Frimat L, *et al*. An initial report from the French SOT COVID Registry suggests high mortality due to Covid-19 in recipients of kidney transplants Kidney Int 2020;98:1549-58.
10. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, *et al*. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On

behalf of the Working Group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707-10.
11. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, *et al*. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26:1793-800.
12. Pan Y, Xia L, Wang Y, Guan H. Dynamic changes in computed tomography manifestations of 105 patients with novel coronavirus pneumonia in Wuhan, China. J Int Med Res 2020;48:300060520972913.
13. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, *et al*. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney Int 2020;97:1083-8.
14. Akalin E, Azzi Y, Bartash R, Seethamraju, H., Parides, M., Hemmige, V. *et al*. Covid-19 and kidney transplantation. N Engl J Med 2020;382:2475-7.
15. Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, *et al*. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. Am J Transplant 2020;20:1800-8.
16. Cravedi P, Mothi SS, Azzi Y, Haverly M, Farouk SS, Pérez-Sáez MJ, *et al*. COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium. Am J Transplant 2020;20:3140-8.
17. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al*. China medical treatment expert group for Covid-19: Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
18. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, *et al*. Clinical Characteristics of Covid-19 in New York City. N Engl J Med 2020;382:2372-4.
19. Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol 2020;18:1636-7.
20. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, *et al*. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms Gut 2020;69:1002-9.
21. Taneri PE, Gómez-Ochoa SA, Llanaj E, *et al*. Anemia and iron metabolism in COVID-19: A systematic review and meta-analysis. Eur J Epidemiol 2020;35:763-773. doi: 10.1007/s10654-020-00678-5.
22. Cavezzi A, Troiani E, Corrao S. COVID-19: Hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin Pract 2020;10:1271.
23. Chen TY, Farghaly S, Cham S, Tatem LL, Sin JH, Rauda R, *et al*. COVID-19 pneumonia in kidney transplant recipients: Focus on immunosuppression management. Transpl Infect Dis 2020;22:e13378.
24. Farouk SS, Fiaccadori E, Cravedi P, Campbell KN. COVID-19 and the kidney: what we think we know so far and what we don't. J Nephrol 2020;33:1213-1218. doi: 10.1007/s40620-020-00789-y
25. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural evidence for direct renal infection with SARS-CoV-2. J Am Soc Nephrol 2020;31:1683-7.
26. Liu X, Wang J, Xu X, Liao G, Chen Y, Hu CH. Patterns of IgG and IgM antibody response in COVID-19 patients. Emerg Microbes Infect 2020;9:1269-74.

Supplementary Table 1: Clinical presentation (Symptoms)

Symptoms	Total (*n*=60)
Cough	35 (58.33%)
Sore-throat	22 (36.70%)
Rhinorrhea	9 (15%)
Chills/rigors	30 (50%)
Nausea/Vomiting	21 (35%)
Abdominal pain	5 (8.34%)
Headache	20 (33.34%)
Myalgia	37 (61.67%)
Fatigue	45 (75%)
Confusion	5 (8.33%)
Chest pain/pressure	12 (20%)
Loss of smell	20 (33.34%)
Loss of taste	29 (48.33%)
Cheilitis, glossitis, oral ulcer	16 (26.67%)

Supplementary Table 2: Trends of tacrolimus trough levels (C_0) during COVID-19 as compared with historical C_0 levels

Current C_0 Level (ng/mL)	Current Dose-Adjusted C_0 Level	Last Documented Dose-Adjusted C_0 Level	Supratherapeutic C_0 Level	COVID-19 Associated Rise in Dose--Adjusted C_0 Level	Diarrhea During COVID-19	CYP3A5 status
12.6	14.17	9.11	Present	Present	Absent	*3/*3
8.8	16.89	17.6	Present	Absent	Present	*3/*3
8.3	10.79	5.08	Present	Present	Present	*1/*3
24.5	35.9	4.79	Present	Present	Absent	*3/*3
8.52	25.1	23.2	Present	Present	Present	*3/*3
4.19	8.49	19.74	Absent	Absent	Present	*3/*3
7.52	44.33	18.76	Present	Present	Present	*3/*3
4.8	6.66	8.72	Absent	Absent	Present	*1/*3
1.0	2.92		Absent	Absent	Present	
7.7	22.9	23.17	Present	Absent	Present	
5.2	17.3	19.98	Absent	Absent	Absent	*3/*3
<2	5.6	3.57	Absent	Absent	Absent	
6.20	16.12	—	Absent	Absent	Present	
16	48	—	Present	Present	Present	
<2	7	—	Absent	Absent	Present	
16.5	110	22.36	Present	Present	Present	*3/*3
2.91	2.98	3.55	Absent	Absent	Present	*1/*1
>30	98.4	28.8	Present	Present	Present	*3/*3
2.48	6.15	17.18	Absent	Absent	Absent	*1/*3
4.31	7.7	17.8	Absent	Absent	Absent	
7.13	33.35	29.2	Present	Present	Present	
4.18	9.55	16.7	Absent	Absent	Present	
7.84	7.62	4.58	Present	Present	Absent	*1/*1
3.29	4.6	5.07	Absent	Absent	Present	*1/*1
3.2	8.06	10.2	Absent	Absent	Absent	
5.4	13.5	11.6	Absent	Absent	Absent	
5.92	7.55	8.42	Absent	Absent	Present	*1/*3
6.68	13.36	10	Absent	Absent	Absent	*3/*3
6.48	9.25	9.45	Absent	Absent	Absent	
4.82	9.6	—	Absent	Absent	Present	*3/*3
8.4	14.2	—	Present	—	Present	
6.1	9.4	—	Absent	—	Present	
3.01	4.13	—	Absent	—	Absent	
2.87	3.58	—	Absent	—	Present	
3.23	6.46	—	Absent	—	Present	

COVID-19 - coronavirus disease 2019; CYP3A5 - Cytochrome P450 Family 3 Subfamily A Member 5. *Dose-adjusted C_0 level=level adjusted for 0.1 mg/kg dose=Level (ng/mL) × Current Weight (kg) × 0.1/Dose (mg)

Supplementary Table 3: RT-PCR positivity and anti-COVID-19 antibodies

RT-PCR	IgM	IgG
Negative at d21	Positive on d24	Positive on d24
Positive at d26	Positive on d21	Positive on d21
Positive at d16	Positive from d9 till d38	Positive on d38
Positive at d17	Negative on d18	Positive on d18
Positive at d29	Negative till d69	Negative till d69
Positive at d21	Negative on d16	Positive on d15
Positive at d21	Positive on d20	Positive on d20
Negative at d16	Negative on d18	Positive on d18
Positive at d14	Positive on d15	Positive on d15
Positive at d16	Positive on d15	Positive on d15
Negative at d21	Positive on d15	Positive on d15
Positive at d17	Positive on d16	Positive on d16
Positive at d16	Negative on d79	Negative on d79
Positive at d21		Negative on d90
Negative at d8		Positive on d15
Negative at d7		Positive on d15
Negative at d12		Positive on d15
—	Positive on d29	Positive on d29
Positive at d8		Positive on d18
Negative at d12		Positive on d15
Positive at d14		Positive on d15
Positive at d7		Positive on d15
Negative at d8		Positive on d14
Negative throughout the course	Positive on d9	
Not repeated		Positive at d15
Negative on d8		Positive on d15
Positive at d8		Positive on d28
Negative at d8		Positive at d30
Not repeated		Negative till d28
Negative at d6		Positive at d30
Positive at d15		Positive at d15
Negative at d12		Positive at d15
Positive at d15		Positive on d15
Negative at d5		Negative at d15
Positive at d8		Negative at d15
Positive at d8		Positive at d15
Positive at d8		Positive at d21

COVID-19 - coronavirus disease 2019; RT-PCR - reverse transcription-polymerase chain reaction; Ig - immunoglobulin; d - day