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# Better outcome of COVID-19 positive kidney transplant recipients during the unremitting stage with optimized anticoagulation and immunosuppression

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## Abstract

**Introduction:** COVID-19 is an ongoing pandemic with high morbidity and mortality and with a reported high risk of severe disease in kidney transplant recipients (KTR).

**Aim:** We aimed to report the largest number of COVID-19-positive cases in KTR in a single center and to discuss their demographics, management, and evolution.

**Methods:** We enrolled all the two thousand KTR followed up in our center in Kuwait and collected the data of all COVID-19-positive KTR (104) from the start of the outbreak till the end of July 2020 and have reported the clinical features, management details, and both patient and graft outcomes.

**Results:** Out of the one hundred and four cases reported, most of them were males aged 49.3 ± 14.7 years. Eighty-two of them needed hospitalization, of which thirty-one were managed in the intensive care unit (ICU). Main comorbidities among these patients were hypertension in 64.4%, diabetes in 51%, and ischemic heart disease in 20.2%. Management strategies included anticoagulation in 56.7%, withdrawal of antimetabolites in 54.8%, calcineurin inhibitor (CNI) withdrawal in 33.7%, the addition of antibiotics in 57.7%, Tocilizumab in 8.7%, and antivirals in 16.3%. During a follow-up of 30 days, the reported number of acute kidney injury (AKI) was 28.7%, respiratory failure requiring oxygen therapy 46.2%, and overall mortality rate was 10.6% with hospital mortality of 13.4% including an ICU mortality rate of 35.5%.

**Conclusion:** Better outcome of COVID-19-positive KTR in our cohort during this unremitting stage could be due to the younger age of patients and early optimized management of anticoagulation, modification of immunosuppression, and prompt

Clinical trial notation: This trial had approved by Kuwait ministry of health (2020/1481) and registered in Clinicaltrial.gov (NCT04542954).

treatment of secondary bacterial infections. Mild cases can successfully be managed at home without any change in immunosuppression.

**KEYWORDS**
antibiotic: antiviral, antiproliferative agent, COVID-19 in Kidney transplants, immunosuppressant, infection and infectious agents, kidney (allograft) function/dysfunction, kidney disease: infectious, viral

## 1 | INTRODUCTION

Since the end of 2019, the novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) has been transmitted from Wuhan, China to most of the countries.[1] The resulting disease, coronavirus disease 2019 (COVID-19), has been categorized as a global pandemic. The published experience from China and other countries on COVID-19 has highlighted the clinical characteristics of the virus, with special stress on risk factors and prognosis, in the general population. But, there is limited data about COVID-19 in immunocompromised individuals, particularly kidney transplant recipients.[2]

It was noted that the viral burden and patient mortality rate were higher in infected transplant cases with past epidemics of coronavirus,[3] because of an impaired immunity, especially those with other medical comorbidities.

Transplant recipients, with compromised T-cell immunity, represent a group of patients who are more susceptible to develop COVID-19 because of their poor immunity that make them vulnerable to opportunistic infections. Till the end of August 2020, prevention is the main strategic plan, because of the lack of valid treatment or vaccine. Kidney transplantation programs were temporarily halted during this pandemic in many centers, particularly for high-risk elderly recipients with medical comorbidities. Strict compliance to handwashing, safe distancing, and regular virtual/telephonic evaluation of transplant patients were being carried out in many centers to reduce the prevalence and for the safe management of mild to moderate cases. The COVID-19 United Kingdom (UK) register was very resourceful in the management of difficult cases during these challenging times.[2,4,5]

The first series of COVID-19-positive KTR (seven cases) came from south London, United Kingdom,[4] while the second series (twenty cases) reported from Brescia, Italy.[6] In the series from the United Kingdom, they reduced the immunosuppressive agents in combination with general supportive therapy without specific antiviral therapies.

Alberici et al[6] in their series, withdrew baseline immunosuppression in all patients. They added methylprednisolone in a dose of 16 mg per day, among nineteen out of twenty cases in addition to antiviral therapy and hydroxychloroquine (HCQ). They also used Tocilizumab (humanized anti-interleukin-6 receptor monoclonal antibody) in six of their patients along with dexamethasone to combat the uncontrolled cytokine release that developed in critically ill patients with acute respiratory distress syndrome (ARDS). They reported a mortality rate of 25% and AKI in 6 patients including one patient needing hemodialysis.

The prevalence of COVID-19-positive KTR during the period of pandemic is not well evaluated and the optimal management of these cases is not yet well-defined. In this setting, we undertook this study in our center, Organ Transplant Centre, Hamed Al Essa, Kuwait.

## 2 | AIM OF THE STUDY

We aimed to study the COVID-19-positive kidney transplants and to evaluate their demographics, management, and outcome.

## 3 | PATIENTS AND METHODS

We have a single renal transplant center in Kuwait where nearly 2000 KTR are followed up. We collected the data from COVID-19-positive kidney transplants that were diagnosed in all governmental hospitals from the first week of March 2020 till August 1, 2020. All COVID-19-positive adult KTR with a functioning allograft who presented to the causality and were either discharged or hospitalized were included. Clinical features, details of management, and both patient and graft outcomes were recorded. Patients' data were collected from the electronic database of both the parent transplant center and isolation hospitals where COVID −19 cases were managed. Patient characteristics were compared in two periods of time; first period between March till the end of May 2020 and the second period during the next 2 months.

### 3.1 | Laboratory diagnosis

COVID-19 diagnosis was confirmed by a positive result on real-time polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab specimens targeting the RNA-dependent RNA polymerase gene using amplification according to the manufacturer's recommendation. All electronic files on the database system were carefully revised for collection of patients' demographics, specifically the original kidney disease, type of dialysis, immediate graft function status, immunosuppressive agents, and other data especially the history of recent exposure, immunosuppression changes, clinical features suggesting COVID-19, and laboratory results with special stress on serum creatinine, liver function tests,

procalcitonin (PCT), C-reactive protein (CRP), D-dimer, and complete blood count. AKI was considered and categorized according to Kidney Disease Improving Global Outcomes (KDIGO) criteria. AKI was staged for severity according to the following criteria: Stage 1 when creatinine was ranging between 1.5: <2 folds of baseline; stage 2 if the creatinine was ranging between 2: <3 folds, and stage 3 if creatinine was more than 3 folds of the baseline. The study was approved by the ethical committee of the Ministry of Health of Kuwait.

### 3.2 | Radiological assessment

The presence of a radiological abnormality was determined based on the descriptive documentation in medical charts of infected patients and when imaging scans were available, they were reviewed by the attending chest physician. A third reviewer opinion was taken if a major disagreement between the two initial reviewers happened. The degree of severity of COVID-19 (non-severe vs. severe) at the time of hospital admission was defined using the American Thoracic Society (ATS) guidelines for community-acquired pneumonia.[7]

### 3.3 | Statistics

Statistical analyses were performed using Statistical Package for the Social Sciences version 20.0 (SPSS). Qualitative data were presented as numbers and percentages, while quantitative variables were presented as means ± standard deviation and median. We used a T test to compare the means and standard deviations of the studied groups. Categorical variables were compared using the chi-squared test. *p*-values were considered significant if <.05.

## 4 | RESULTS

In our study, 104 kidney transplants were confirmed as COVID-19 positive by PCR test and all of them were symptomatic. Eighty-two (78.8%) of these patients required hospital admission. Out of the eighty-two, thirty-one cases (37.8%) needed active care in the ICU and thirteen among these ICU patients required invasive ventilation. Eleven of the 104 (10.6%) patients who were COVID-19 positive, died during this period.

### 4.1 | Demographics

The mean age of COVID-19-positive cases was 49.3 ± 14.7 years. (Patient demographics are summarized in Table 1) Most of the patients were males 78 (75%) and 55 (52.9%). The original kidney disease in most patients with COVID-19 was diabetic nephropathy (17.3%) and glomerulonephritis (17.3%). Most of the patients received their grafts from live donors after a variable period of hemodialysis. The majority of them received either lymphocyte depleting or non-depleting agents as induction immunosuppression (42.3%) and were maintained on Tacrolimus-based immunosuppression (59.6%). Only 6 patients are current smokers.

The mean duration from transplant date to COVID-19-positive testing was 113 ± 166 months (median 72 months) with minimal duration of 1.37 months and the longest duration of 1397.7 months (Table 1).

### 4.2 | Characteristics of the studied COVID-19 patients

The characteristics of the study population are listed in Table 1. The most frequent presenting symptoms of COVID-19 patients were fever (74%), cough (61.5%), and shortness of breath (37.5) followed by sore throat (19.2%), myalgia (32.7%), and gastrointestinal symptoms (21.2%). Most patients (93 out of 104) had X-ray chest (CXR) performed at the time of COVID-19 diagnosis, (82 out of hospital admissions and 11 out of 22 who needed home isolation) and more than 72% had high resolution computed tomography of the chest (HRCT). The findings obtained by X-ray and HRCT chest scan showed bilateral multifocal patchy opacities matching with COVID-19 pneumonia in 55 cases (52.9%). However, radiological features were not typical of COVID-19 in 18 cases: lobar consolidation in 15 cases, effusion in 1, cavity lesion in 1, and reticular infiltrate in 1.

We did not have any coexisting viral infections; but eleven patients (Table 2) showed features suggestive of bacterial co-infection as evidenced by high WBCS, PCT, and or positive cultures and sixty of our patients received empirical antibacterial therapy during their hospital stay. Most of our patients (56.7%) started early anticoagulation (Table 1).

Allograft function was stable in 88 (84.6%) patients. AKI was reported in thirty patients: six with stage 3, seven with stage 2, and seventeen with stage 1. (Table 1) Six patients developed oligo-anuria needing renal replacement therapy using continuous venovenous hemodiafiltration (CVVHDF) due to hyperkalemia (2 cases), hypervolemia (2 cases) and both conditions in the remaining 2 cases (Table 3).

At the time of hospital admission, leukopenia (less than 4000 cells/microliter) was confirmed in 18.3% of patients while the mean levels of CRP, D-dimer, and ferritin were reported as 119 ± 159, 1397 ± 3919, and 648 ± 543, respectively (Table 2).

Though more than 53% of patients did not need oxygen support, non-invasive and invasive ventilation was needed in 48 cases in the ICU (47.2% of cases). Only one patient was managed by ECMO (Tables 1, 3).

From Table 3, it can be noted that majority of the hospitalized patients were older than 50 years, had ischemic heart disease, and presented with fever and dyspnea with bilateral radiologic findings ($p < .05$). Most ICU admissions were in COVID-19 isolation hospitals and they had all COVID-19 risk factors ($p < .05$) and presented with cough, dyspnea, and bilateral radiological findings compatible with COVID-19 ($p < .05$). AKI was also more prevalent

**TABLE 1** Demographics and clinical characteristics of COVID-19-positive Kidney transplant recipients

| *N* = 104 | Frequency (*N* = 104) | % |
|---|---|---|
| Isolation area | | |
| General hospital | 82 | 78.8 |
| Home | 22 | 21.2 |
| Intensive care unit admission | 31 | 29.8 |
| Donor mean age ± SD (years) | 44 ± 5.2 | |
| Recipient mean age ± SD (years) | 49.3 ± 14.7 | |
| Mean age of mortality recipients ±SD (years) | 56.5 ± 15 | |
| Mean age of surviving recipients ±SD (years) | 48.6 ± 13.7 | |
| Donor type (living /cadaveric) | 90/14 | 86.5/13.5 |
| Immunosuppression | | |
| Induction | | |
| None | 3 | 2.9 |
| Simulect | 37 | 35.6 |
| Lymphocyte depleting agents | 40 | 38.5 |
| Unknown | 24 | 23 |
| Maintenance | | |
| Cyclosporine based | 29 | 27.9 |
| Tacrolimus based | 62 | 59.6 |
| Steroids | 103 | 99 |
| Mycopholate mofetil or sodium (MMF or MPA) | 90 | 86.5 |
| Sirolimus | 4 | 3.8 |
| Azathioprine | 5 | 4.8 |
| Immunosuppression plan | | |
| No change | 47 | 45.2 |
| Hold antiproliferative (MMF or MPA) | 22 | 21.1 |
| Hold antiproliferative and calcineurin inhibitors (CNI) | 11 | 10.6 |
| Hold antiproliferative, CNI, and increased steroid | 24 | 23.1 |
| COVID-19 risk factors | | |
| Diabetes | 51 | 51 |
| Hypertension | 67 | 64.4 |
| Ischemic heart disease | 21 | 20.2 |
| Pulmonary disease | 9 | 8.7 |
| Obesity (bariatric surgery) | 2 | 1.9 |
| Obesity | 6 | 5.7 |
| Others | 8 | 7.7 |
| Clinical presentation | | |
| Fever | 77 | 74 |
| Cough | 64 | 61.5 |
| Shortness of breath | 39 | 37.5 |
| Body aches | 34 | 32.7 |
| GIT symptoms | 22 | 21.2 |
| Sore throat | 20 | 19.2 |
| Chest X-ray findings | | |
| Normal | 25 | 24 |
| Unilateral | 4 | 3.8 |
| Bilateral | 64 | 61.6 |
| Not done | 11 | 10.6 |
| High resolution computed tomography (HRCT) chest | | |
| Not done | 29 | 27.9 |
| Synchronized with COVID-19 | 55 | 52.9 |
| Non-synchronized with COVID-19 | 18 | 17.3 |
| Others | 2 | 2 |
| Bacterial co-infection | 11 | 10.57 |
| Oxygen requirement | | |
| No oxygen needed | 56 | 53.8 |
| Nasal cannula and masks | 35 | 33.7 |
| Invasive oxygen (ventilator) | 12 | 11.5 |
| Invasive oxygen (ECMO) | 1 | 1 |
| Management plan | | |
| Heparin | 59 | 56.7 |
| Steroid (higher dose or pulse therapy) | 33 | 31.7 |
| Antibacterial | 60 | 57.7 |
| Antiviral | 17 | 16.3 |
| Tamiflu | 9 | 8.6 |
| Non-Tamiflu agents | 8 | 7.7 |
| Antifungal | 3 | 2.9 |
| Biological agents | 9 | 8.7 |
| Renal graft affection | | |
| Acute kidney injury: | 30 | 28.8 |
| Stage 1 (rising creatinine 1.5–2 folds) | 17 | 16.3 |
| Stage 2 (rising creatinine 2–3 folds) | 7 | 6.7 |
| Stage 3 (rising creatinine >3 folds) | 6 | 5.7 |
| Indications for dialysis (CVVHDF)* | | |
| Hyperkalemia | 2 | 1.9 |
| Fluid overload | 2 | 1.9 |
| Both | 2 | 1.9 |
| Graft outcome | | |
| Functioning graft | 88 | 84.6 |
| Failed graft | 4 | 3.8 |
| Impaired graft (more than 25% of baseline value) | 12 | 11.5 |
| Patient outcome: (living/dead) | 93/11 | 89.4/10.6 |
| Hospital stay in days (mean ± SD) (median, range) | 18.6 ± 19.5 (12.9, 135) | |
| Duration from transplant to COVID-19 in months (mean ± SD) (median, range) | 99.8 ± 83 (72, 317) | |

(Continues)

*(CVVHDF)* = continuous venovenous hemodiafiltration.

**TABLE 2** Showed biochemical parameters of the studied patients at the time of admission

| | Mean ± standard deviation | Median/range |
|---|---|---|
| Age in years | 48.5 ± 14 | 51 (57) |
| Weight in kg | 75 ± 27 | 75 (128) |
| eGFR (admission) | 59.7 ± 29.7 | |
| eGFR (discharge) | 80.7 ± 77 | |
| Admission eGFR (cases without acute kidney injury) | 72.15 ± 29.9 | |
| Discharge eGFR (cases without acute kidney injury) | 100.35 ± 93.7 | |
| White blood cell count | 7100 ± 500 | 6100 (13 600) |
| Lymphocytes | 0.34 ± 0.7 | 1.3 (4410) |
| D-dimer | 1397 ± 3919 | 466 (21 456) |
| C- reactive protein | 119 ± 159 | 76 (919) |
| Ferritin | 648 ± 543 | 497 (1781) |
| Alanine aminotransferase (u/ml) | 50 ± 121 | 20 (667) |
| Vitamin D level (pgm/ml) | 29.9 ± 26 | 23 |
| Isolated microorganisms in transplant recipients | Organism | Sample, others |
| Patient 1: | Pseudomonas aeruginosa | (MRD, rectal swab) |
| Patient 2: | Klebsiella Pn. (MDR), Pseudomonas aeruginosa | (Urine, blood) |
| Patient 3: | Klebsiella Pn., stenotrophomonas | (Blood) |
| Patient 4: | Klebsiella Pn. (MDR) | (Blood) |
| Patient 5: | Stenotrophomonas maltophilia (MDR) | (ETT) |
| Patient 6: | Acinetobacter (MDR) | Urine and ETT |
| Patient 7: | Pseudomonas aeruginosa | (Blood) |
| Patient 8: | Pseudomonas aeruginosa | ETT |
| Patient 9: | Pseudomonas aeruginosa | Throat, blood |
| Patient 10: | Ecoli (MDR) | Blood |
| Patient 11: | Staph. hemolyticus | Blood |

*eGFR, Estimated glomerular filtration rate; MDR, multidrug resistant; ETT, endotracheal secretion.

in ICU patients and they had significantly poorer patient and graft outcomes ($p < .05$).

At the end of the follow-up, ninety-three patients were alive (88 with functioning grafts, 4 with failed and 12 with impaired grafts, Table 2) while eleven ICU patients died (3 with functioning grafts, 3 with failed grafts, and 5 with impaired grafts, Table 4). We did not perform any kidney biopsy during hospitalization. The mean hospital stay was 17.5 ± 19.8 days (median was 13 days' range) while the median follow-up for our cohort was 30 days (Table 2).

### 4.3 | Immunosuppressive regimen

Baseline immunosuppressive (IS) regimens and their modifications are summarized at the end of Table 1, Figure 2. At the time of COVID-19 presentation, twenty-nine cases were maintained on a cyclosporine-based regimen while sixty-two cases were maintained on Tacrolimus-based therapy. As can be seen in Table 4, the same IS regimen was continued in 47 patients (45.2%); anti-proliferative drugs (MMF, mTOR inhibitors, or azathioprine) were held alone in 22 cases (21.1%) or both anti-proliferative drugs and CNI were discontinued during the period of hospitalization in 11 cases (10.6%). Together with the last regimen, steroid dosage was increased in 57 cases (54.8%). After being discharged home, the baseline IS regimen was resumed within the next week. The majority of patients who continued their maintenance IS regimen ($n = 47$) were males and isolated at home or in a field hospital (with CNI trough levels similar to the baseline values) while those with modified IS regimen ($n = 57$) were dyspneic females (with higher prevalence of hypertension and ischemic heart disease) and were quarantined in isolation hospital (Table 4, $p < .05$). Diabetic patients and those with chronic chest disease were comparable in the two groups ($p > .05$). Most of the patients with reduced

**TABLE 3** ICU vs. non-ICU COVID-19 patients in relation to risk factors and clinical outcome

| *N* = 104 | Non-ICU cases (*N* = 73) % | ICU cases (*N* = 31) % | *p*-value |
|---|---|---|---|
| Isolation area | | | |
| General hospital | 51 (69.9) | 31 (100.0) | |
| Home | 22 (30.1) | 0 (0) | .001 |
| Gender | | | |
| Male | 54 (74.0) | 24 (77.4) | |
| Female | 19 (26) | 7 (22.6) | .71 |
| Age groups | | | |
| <50 years | 40 (54.8) | 11 (35.5) | |
| >50 years | 33 (45.2) | 20 (64.5) | .07 |
| Nationality | | | |
| Kuwaiti | 37 (50.7) | 18 (58.1) | |
| Non-Kuwaiti | 36 (49.3) | 13 (41.9) | .49 |
| COVID-19 risk factors | | | |
| Diabetes mellitus | 31 (42.5) | 20 (64.5) | .04 |
| Hypertension | 42 (57.5) | 25 (80.65) | .024 |
| Ischemic heart disease | 10 (13.7) | 11 (35.5) | .011 |
| Pulmonary disease | 3 (4.1) | 6 (19.4) | .011 |
| Clinical presentation | | | |
| Fever | 51 (73.9) | 26 (83.9) | .27 |
| Sore throat | 12 (17.4) | 8 (25.8) | .33 |
| Cough | 38 (55.1) | 26 (83.9) | .006 |
| Shortness of breath | 19 (27.5) | 20 (64.5) | <.001 |
| Gastrointestinal symptoms | 13 (18.8) | 9 (29.0) | .25 |
| Body aches | 25 (36.2) | 9 (29.0) | .48 |
| Chest X-ray findings | | | |
| Not done | 11 (15.1) | 0 (0) | |
| Unilateral | 3 (4.1) | 1 (3.2) | |
| Bilateral | 36 (49.3) | 28 (90.38) | |
| Normal | 23 (31.5) | 2 (6.5) | .001 |
| High resolution computed tomography (HRCT) chest | | | |
| Not done | 27 (37.0) | 2 (6.5) | |
| Synchronized with COVID-19 | 31 (42.5) | 24 (77.4) | |
| Non-synchronized with COVID-19 | 14 (19.2) | 4 (12.9) | .004 |
| Renal graft affection | | | |
| Acute kidney injury | | | |
| Normal | 64 (87.7) | 10 (32.3) | |
| Stage 1 (rising creatinine 1.5–2 folds) | 7 (9.6) | 10 (32.3) | |
| Stage 2 (rising creatinine 2–3 folds) | 2 (2.7) | 5 (16.1) | |
| Stage 3 (rising creatinine >3 folds) | 0 (0) | 6 (19.4) | <.001 |
| Graft outcome | | | |
| Functioning graft | 67 (91.8) | 21 (67.7) | |
| Failed graft | 1 (1.4) | 3 (9.7) | |
| Impaired graft (more than 25% of baseline value) | 5 (6.8) | 7 (22.6) | .007 |
| Patient outcome | | | |
| Living | 73 (100) | 20 (64.5) | |
| Dead | 0 | 11 (35.5) | <.001 |

IS regimen showed HRCT chest findings compatible with COVID-19 ($p$ = .02). We observed that AKI was significantly higher in patients with changed IS regimens ($p$ = .003) and this was reflected on patient outcome and to a lesser extent on graft outcome.

### 4.4 | Rate of COVID-19 infection

The present study of COVID-19 infection among our KTR has been done covering 2 periods starting from the beginning of March till the end of July 2020. The first is a period of three months from 1st of March till the end of May, 2020, which is compared to the second period of 2 months of June and July 2020, (Figure 1) studying in detail on their demographics, management, and outcomes. We found that the two groups were comparable regarding the COVID-19 risk factors, presenting features, radiological findings, management plan, and outcome ($p$ > .05). We found a trend toward an increase in the number of infected patients with a peak in last June (59 in the second period vs. 45 cases in the first period, $p$ = .052) and a significantly increasing number of late infected females (20 vs. 6) ($p$ = .016).

### 4.5 | Additive treatment

Among the hospitalized cases, low molecular weight heparin was started in 59 cases (56.7%) and an additional antibacterial (mono-or combined therapy) was given in 60 (57.7%) cases and this was including piperacillin/tazobactam, azithromycin, ceftriaxone, levofloxacin, cefepime, and vancomycin.

## 5 | DISCUSSION

During the early months of 2020, COVID-19 had spread out from China to most of the world countries[1] and most of the population had a direct or indirect risk to catch infection. Patients with kidney

**TABLE 4** Showed the impact of immunosuppression change among the studied patients

| *N* = 104 | Unchanged immunosuppression *N* (47) % | Changed immunosuppression *N* (57) % | *p*-value |
|---|---|---|---|
| Isolation area | | | |
| General hospital | 29 (59.3) | 53 (92.8) | .0001 |
| Home | 18 (38.3) | 4 (7) | .0001 |
| Gender | | | |
| Male | 40 (85.1) | 38 (66.7) | |
| Female | 7 (14.9) | 19 (54.8) | .03 |
| Age groups | | | |
| <50 years | 27 | 24 | |
| >50 years | 20 | 33 | **.11** |
| Nationality | | | |
| Kuwaiti | 19 | 36 | |
| Egyptian | 4 | 9 | |
| Indian | 9 | 2 | |
| Pakistani and Bangladeshi | 7 | 3 | |
| Others | 8 | 7 | .014 |
| COVID-19 risk factors: | | | |
| Diabetes mellitus | 21 (44.7) | 30 (52.6) | .42 |
| Hypertension | 22 (46.8) | 45 (78.9) | .001 |
| Ischemic heart disease | 5 (10.6) | 16 (28.1) | .028 |
| Pulmonary disease | 3 (6.4) | 6 (10.5) | .45 |
| Clinical presentation: | | | |
| Fever | 30 (69.8) | 47 (82.5) | .13 |
| Sore throat | 8 (18.6) | 12 (21.1) | .76 |
| Cough | 23 (53.5) | 41 (71.9) | .057 |
| Shortness of breath | 10 (23.3) | 29 (50.9) | .005 |
| Gastrointestinal symptoms | 7 (16.3) | 15 (26.3) | .23 |
| Body aches | 11 (25.6) | 23 (40.4) | .12 |
| Chest X-ray findings | | | |
| Not done | 10 (21.3) | 1 (1.8) | |
| Unilateral | 1 (2.1) | 3 (5.3) | |
| Bilateral | 23 (48.9) | 41 (71.9) | |
| Normal | 13 (27.7) | 12 (21.1) | .006 |
| High resolution computed tomography (HRCT) chest | | | |
| Not done | 20 (42.6) | 9 (15.8) | |
| Synchronized with COVID-19 | 19 (40.4) | 36 (63.2) | |
| Non-synchronized with COVID-19 | 1 (2.1) | 1 (1.8) | .022 |
| Management plan: | | | |
| Heparin | 18 (38.3) | 41 (71.9) | .001 |
| Steroid (higher dose or pulse therapy) | 2 (4.3) | 31 (54.4) | <.001 |
| Antibacterial | 16 (34) | 44 (77.2) | <.001 |
| Antiviral | 1 (2.1) | 10 (17.5) | .011 |
| Renal graft affection (Acute kidney injury) | | | |
| Normal | 42 (89.4) | 32 (54.4) | |
| Stage 1 (rising creatinine 1.5–2 folds) | 2 (4.3) | 15 (26.3) | |
| Stage 2 (rising creatinine 2–3 folds) | 2 (4.3) | 5 (8.8) | |

(Continues)

**TABLE 4** (Continued)

| *N* = 104 | Unchanged immunosuppression *N* (47) % | Changed immunosuppression *N* (57) % | *p*-value |
|---|---|---|---|
| Stage 3 (rising creatinine >3 folds) | 13 (2.1) | 5 (8.8) | .003 |
| Graft outcome | | | |
| Functioning graft | 44 (93.6) | 44 (77.2) | |
| Failed graft | 1 (2.1) | 3 (5.3) | |
| Impaired graft (more than 25% of baseline value) | 2 (4.3) | 10 (17.5) | .066 |
| Patient outcome | | | |
| Living | 47 (100) | 46 (80.7) | |
| Dead | 0 (0) | 11 (19.3) | .001 |

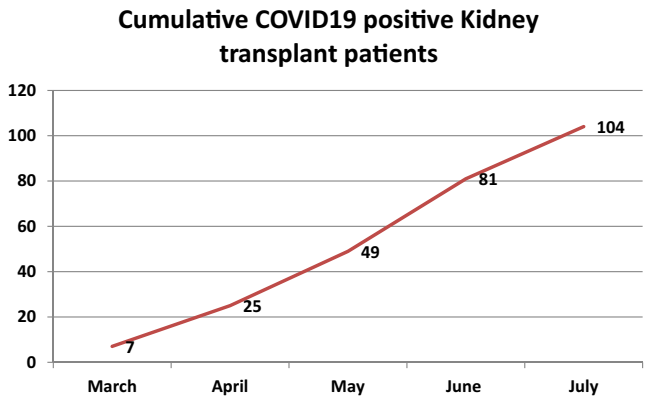


**FIGURE 1** Cumulative COVID-19 kidney transplant cases during the study

transplants were considered to be at particularly high risk for severe COVID-19 disease due to their impaired immune response and concurrent comorbidities.[1]

Our present study of 104 COVID-19-positive KTR has shown that a multidisciplinary approach can efficiently manage such a high-risk group of patients. The median follow-up period of our study was thirty days with a reported total overall case fatality rate of 10.6%, hospitalized case fatality rate of 13.4%, and ICU case fatality rate of 35.5%. In a study from the USA for a similar follow-up period, Lubetzky et al reported a bit higher overall case fatality rate of 13% and hospitalized case fatality rate of 18%.[8] Initial small reports from China denoted that three out of five ICU patients died, which was consistent with the poor prognosis of the general population that required intensive care (52% of patients with ARDS died).[9] Nair et al showed similar poor outcomes with 30% mortality in their case series (12 cases).[10] Zhang et al in another study from China, of 5 COVID-19-positive kidney transplants with non-severe infections, did not report any reported mortalities.[11] In a study from Italy, the overall mortality rate among hospitalized COVID-19-positive transplant recipients was 25%.[6] In another multicenter trial by Carvedi and his colleagues, the reported mortality among COVID-19 transplant recipients was 32%.[12]

The relatively better outcome in our cohort compared to other published smaller cohorts, might be due to the relatively younger mean age (49.3 ± 14.7 years) of our patients, and our adopted management protocol that includes earlier anticoagulation, careful modification of immunosuppressive medications, management of associated bacterial with antibacterial therapy in addition to selective and monitored use of unverified therapies. Larger studies are needed to fully understand the mortality risk of COVID-19-positive transplant recipients.

Jager et al denoted in their multivariate analysis that higher age is the most important mortality risk factor in both dialysis and transplant patients with COVID-19.[13] Similarly, we found a relatively higher mean age of the deceased patients compared to survivors (56.5 ± 15 vs. 48.66 ± 13.7 years, Table 1).

During the period of lockdown, our transplant program was temporarily withheld and patients were being evaluated, as many transplant centers, did via mobile applications. Patients with more severe manifestations were reviewed in the COVID-19 triage area of our hospital (with full use of patient protective equipment) or COVID-19 isolation hospitals, to minimize the risk of infecting other transplant patients. This policy was adopted by many transplant centers.[8]

To the best of our knowledge, this study included a significantly high number of COVID-19-positive KTR with their data collected from their initial contact with the healthcare provider and from the tertiary COVID-19 general hospitals where they were managed.

Most of these patients had their transplant more than a year ago and so the impact of induction therapy has been nullified. Only ten patients out of 104 (9.6%) had their transplant less than a year ago and out of these, two died with impaired graft function and eight were discharged with functioning grafts.

The risk factors for a bad outcome that are reported in the general population included advanced age, male gender, and preexisting comorbidities especially hypertension, diabetes, and ischemic heart disease.[14-16] In our cohort, all hospitalized patients had more comorbidities, unambiguously cardiovascular (hypertension and ischemic heart disease), and more severe symptoms at the time of admission. These patients also had elevated levels of ferritin, D-dimer, PCT, and CRP, which are markers of severe disease and poor prognosis as has been reported in other studies.[17] COVID-19 can present in different clinical manifestations and severity with variable outcomes in KTR. In our study, the most frequent presenting symptoms were high fever, cough, shortness of breath, and body aches. The presenting

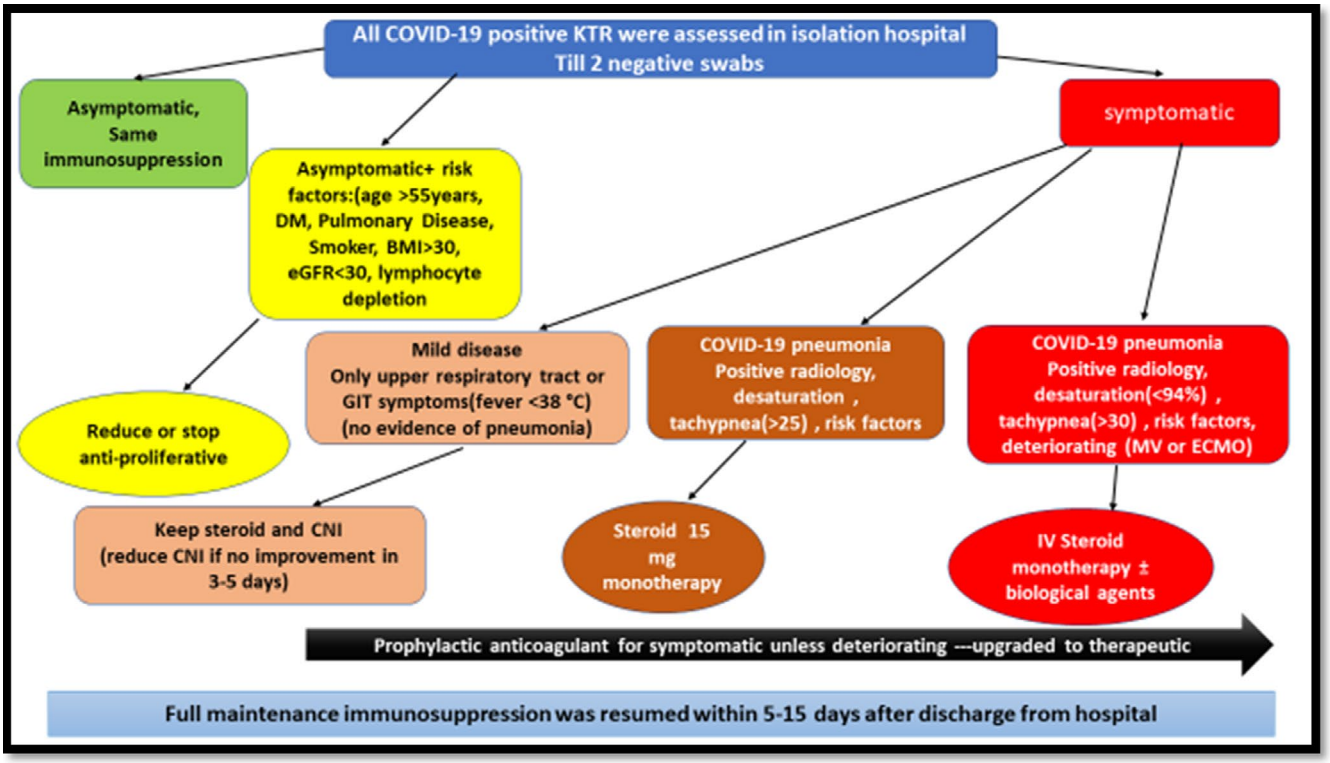


**FIGURE 2** Showed our adopted management protocol of COVID-19-positive kidney transplant recipients

symptoms were comparable to symptoms of non-transplant cases. Most patients had radiological features suggestive of viral broncho-pneumonia on an X-ray or HRCT chest which was considered as moderate to severe illness and despite those features, 53.5% did not need oxygen therapy.[18] Eighty-two (78.8%) of our patients were hospitalized, with thirty-one (29.8%) cases needed admission to the ICU. The mortality rate reported in our cohort is lower than that reported by Lubetzky et al (18% vs. 23.3%, respectively) [8] and much lower than that reported by Goyal et al (28%)[10,12,19,20] and almost similar to the mortality in the general population (10.2%).[21] This difference could be due to the younger mean age among our cohort and our management protocol with earlier anticoagulation and modification of immunosuppressive medications. Moreover, all patients in the ambulatory setting have reported symptom resolution or significant improvement.[8] Manipulating IS medications in COVID-19-positive recipients was arduous and debatable. T-cell mediated immunity is an important mechanism in controlling viral disorders and the consensus was to reduce or withhold antimetabolites like mycophenolic acid.[11,22-24] But data are lacking on the optimal strategy regarding CNI, in the management of COVID-19 cases. In our patients, we planned modification of immunosuppressive drugs depending on the clinical condition of the patients. We adopted a policy of initially modifying the antimetabolites, followed by CNI, guided by the clinical progress of the patient. Many other centers have reported following a similar policy.[22] Zhu et al[25] -in a case series from Wuhan, China- treated successfully nine out of ten KTR by holding both CNI and antimetabolites along with high-dose steroids. Akalin et al[26] withheld antimetabolites in 24 out of 36 patients (86%) and CNI in 6 severe cases (21%). Lubetzky et al[8,12,20] adopted the policy of minimal reduction of CNI targeting a lower Tacrolimus trough for inpatients and holding MMF based on the severity of illness. They did not confirm any case of acute rejection in their study cohort.

In our cohorts, we resumed the full immunosuppressive regimen within one week of discharge. A policy that was matched with that reported by Lubetzky et al[8] who resumed it gradually to the standard levels in their cohort that included 54 kidney transplants, without new readmissions. However, with the lack of kidney graft biopsies among patients with AKI, they did not recognize the true incidence of acute rejection in their study.

There are some studies that have reported in vitro benefits of immunosuppressive agents against COVID-19,[27-30] but in vivo human studies are lacking to back it. In our cohort, we tailored the immunosuppressive drug regimen in a stepwise manner based on the severity of illness and other clinical symptoms. This policy was similar to that suggested by Lubetzky et al[8] who continued immunosuppressive therapy during COVID-19 infection and tailored it depending on the clinical situation.

In our cohort, we observed patient survival was significantly poorer among those who received higher doses of steroid together with discontinuation of either antiproliferative and/or CNI (11 out of 33 cases). This could probably be explained by the fact that these were patients with more severe disease and they were also associated with poor graft outcome. (Table 4). On the contrary, all patients who continued their maintenance immunosuppression recovered fully (47 cases, Table 4). This finding was matched with that reported by Lubetzky et al as well, as 13 of his cohort of 14 hospitalized

patients who continued on MMF and were successfully discharged from the hospital.[8] Moreover, one of the gravest complications of COVID-19 is uncontrolled cytokine release and its consequences. It was reported that CNI may be potentially helpful in their ability to diminish uncontrolled cytokine release through inhibition of nuclear localization of the nuclear factor of activated T cells.[31] This might support the hypothesis that immune-reduction rather than cessation could be beneficial to inhibit cytokine and might explain the relatively lower circulating cytokine levels compared with patients having bacterial sepsis.[32]

Most COVID-19 related mortality is linked with ARDS which is induced by uncontrolled cytokine release.[33,34] Therefore, some form of immunosuppression may be needed in this situation for blockade of Interleukin-6 (IL-6) and interleukin-1 (IL-1). There are studies underway using drugs for blockade of IL-6 and IL-1 in the management of COVID-19.

Majority of our hospitalized patients did not receive hydroxychloroquine (HCQ) because of the lack of sufficient scientific data regarding its efficiency, when prescribed alone or with azithromycin either in mild to moderate cases[35,36] or even as pre-exposure prophylaxis.[37] Moreover, the possible cardiac toxicity of prolonged QT interval and tachyarrhythmias when HCQ is combined with azithromycin has been reported.[38,39] Based on 3 cases who received it in our cohort, we cannot make any conclusions on the use of it in COVID-19 cases.

Part of our management policy (Figure 2) was early use of anticoagulation which was initiated in 59 cases (56.7%), and the use of antibacterial whenever indicated which was in 57.7% of our cases (high PCT, CRP, leukocytosis, or positive cultures). Antiviral agents were given to only 10 patients (9.6%), three of who received oseltamivir, and seven received anti-retroviral agents). We found no significant difference in patient or graft outcomes among those who received antiviral agents vs. those who did not; and between patients who were maintained on oseltamivir vs. other agents ($p > .05$). The initial reports using remdesivir were encouraging in divergence to our results possibly because of the small number of cases. Other ongoing studies in organ transplant recipients are up till now to be reported.[40] Three patients in our study received Tocilizumab, of which one died with impaired graft while the other 2 were discharged with functioning grafts. Other studies failed to show any beneficial effects of Tocilizumab either in preventing intubation or death in moderately ill-hospitalized COVID-19 patients[41] or in showing its superiority over standard care.[42] However, Salama et al showed reduced progression of pneumonia but without a significant positive impact on survival.[43]

In our cohort, AKI was reported in 30 patients (28.8% of all patients, 36.5% of hospitalized patients), which came almost similar to that reposted by Azzi et al[20] (23%) but higher than that reported in the general population (3%-15%). However, the AKI cases reported in our series was lower than that reported by Lubetzky et al, 2020[8] (51%), Carvedi et al[12] (52%), and Nair et al[10] (50%) in their hospitalized transplants. The lower prevalence of AKI in our cohort could be explained by the relatively lower rate of uncontrolled cytokine release and less nephrotoxic agents especially CNI. It is worth mentioning that Tacrolimus bioavailability is increased due to short intestinal transit time with diarrhea in cases of COVID-19.[44] Moreover, an earlier start of anticoagulation might explain the lower rate of AKI in our cohort as hypercoagulation and thrombotic micro-angiopathy was mentioned as one of the multifactorial mechanisms of AKI in such patients.[45,46] The increased number of infected patients during the last two months of the study could be explained by the lack of strict precautions that were followed during the lockdown period of the initial four months of the study.

### 5.1 | Study limitations

This includes the retrospective nature of the study, short-term follow-up, and lack of graft biopsies for cases of AKI.

## 6 | CONCLUSION

During this unremitting COVID-19 pandemic, strict preventive precautions should continue. A coordinated and multidisciplinary approach is ideal for managing COVID-19-positive kidney transplants. Patients with mild symptoms-especially in resources restricted regions can be successfully managed at home with telecommunication for symptom progression with tailoring of immunosuppressive agents to prevent uncontrolled cytokine release. For hospitalized patients, relatively younger age, sensible reduction in immunosuppressive drugs (depending on clinical progression), early anticoagulation, and prompt therapy of co-bacterial infections might be the reasons for our favorable outcome. However, AKI was observed in a considerable percentage of patients that needed hospitalization and the worst prognostic factor was the need for ventilation.

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### CONFLICT OF INTEREST

Authors have no conflict of interest to disclose.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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