Received: 11 May 2020 | Accepted: 13 June 2020

DOI: 10.1111/tid.13378

ORIGINAL REPORT

WILEY

COVID-19 pneumonia in kidney transplant recipients: Focus on immunosuppression management

Tracy Yixin Chen[1] | Sara Farghaly[1] | Samantha Cham[1] | Luis Lantigua Tatem[2] | Jonathan H. Sin[1] | Roberto Rauda[3] | Maria Ribisi[1] | Nabil Sumrani[3]

[1]Department of Pharmacy, SUNY Downstate Health Sciences University Hospital, Brooklyn, New York, USA

[2]Department of Infectious Diseases, SUNY Downstate Health Sciences University Hospital, Brooklyn, New York, USA

[3]Department of Surgery, SUNY Downstate Health Sciences University Hospital, Brooklyn, New York, USA

Correspondence
Tracy Yixin Chen, Department of Pharmacy, SUNY Downstate Health Sciences University Hospital, Brooklyn, NY.
Email: TracyChenTXP@gmail.com

Abstract

Background: The coronavirus disease of 2019, also known as COVID-19, has been declared a global pandemic. Significant controversies exist regarding treatment modalities for this novel disease, especially in immunocompromised patients. Experience with management of COVID-19 in kidney transplant recipients is scarce; effects of this virus on immunosuppressed individuals are not well understood.

Methods: We identified 30 renal transplant recipients with confirmed COVID-19 pneumonia who were admitted to inpatient between March 2020 and April 2020. All patients received a 5-day course of hydroxychloroquine and azithromycin; half of the patients received methylprednisolone. During hospitalization, calcineurin inhibitors and antimetabolites were held; prednisone was continued.

Results: Clinical presentation of flu-like symptoms was similar to those in the general population. Hyponatremia, lymphopenia, acute kidney injury, and elevated inflammatory markers were common. Over the course of follow-up, 23 have been discharged home with a functioning allograft and in stable condition; 4 experienced acute kidney injury requiring renal replacement therapy; 7 patients were intubated, and 6 expired. The mortality rate in our cohort was 20%.

Conclusion: Our findings described the characteristics and outcomes of this highly fatal illness in a multi-ethnic kidney transplant cohort, with insights on immunosuppression management that could further our understanding of this unique disease in immunocompromised populations.

KEYWORDS

COVID-19, immunosuppression, kidney transplantation, viral pneumonia

1 | INTRODUCTION

The coronavirus disease of 2019, also known as COVID-19, has been declared a global pandemic due to its rapid spread and illness severity. As of June 14, 2020, over two million cases of COVID-19 have been reported in the United States, with over 115 000 deaths and counting. New York State in particular has become the epicenter of the virus, with the highest number of reported cases in the world.[1,2] This widespread disease is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a single-stranded

Abbreviations: ACE2, angiotensin-converting enzyme 2; AKI, acute kidney injury; BNP, brain natriuretic peptide; CK, creatine kinase; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ESRD, end-stage renal disease; IFN, interferons; KDIGO, kidney disease improving global outcomes; LDH, lactate dehydrogenase; MERS-CoV, Middle East respiratory syndrome-related coronavirus; PCT, procalcitonin; RT-PCR, real-time reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SCr, serum creatinine; TNF, tumor necrosis factor.

RNA betacoronavirus that binds to angiotensin-converting enzyme 2 (ACE2) receptors, abundant on alveolar cells but also present in kidney, heart, small intestine, and vascular endothelium.[3] Patients may have flu-like symptoms such as fever, shortness of breath, and cough. As the infection advances, viral replication and inflammation of the lung become evident; patients develop viral pneumonia and possibly hypoxia. The most advanced disease manifests as respiratory failure leading to cardiopulmonary collapse.

Transplant recipients are in a vulnerable position in this potentially fatal pandemic. The immunocompromised state predisposes patients to greater susceptibility to infections, more rapid progression to pneumonia, and greater disease severity.[4] In face of debatable treatment options available for COVID-19, strategies for supportive treatment and management of immunosuppression have become focus of care in the transplant population. A case series of 90 solid organ transplant recipients with COVID-19 infection reported a 24% inpatient mortality rate across all organ types, with the immunosuppression reduction strategy of reducing or holding antimetabolites.[5] A brief correspondence on kidney transplant recipients hospitalized with COVID-19 pneumonia reported 35% mortality rate, withholding only antimetabolites primarily.[6] Another similar cohort in which all baseline immunosuppression was withdrawn and only methylprednisolone was administered reported 25% mortality rate.[7] Given the limited information available for the management of immunosuppression in COVID-19 pneumonia, transplant centers are deriving institution-driven protocols for transplant recipients and treating based on experience with other viral infections.

In addition, effects of COVID-19 on ethnic groups have been suggested as a disproportionate burden of illness and death. New York City reported a substantially higher mortality rates among Black/African American patients (92.3 deaths per 100 000 population) and Hispanic patients (74.3 deaths per 100 000 population) compared to other ethnic groups.[8] To date, there are no studies in the United States describing outcomes in a multi-ethnic cohort of kidney transplant recipients with COVID-19 pneumonia, uniformly managed with withholding calcineurin inhibitors and antimetabolites. The objectives of this study are to describe the characteristics of kidney transplant recipients with confirmed COVID-19 pneumonia in a New York City kidney transplant center designated as a COVID-19 only facility, with a focused discussion of immunosuppression and clinical outcomes of this potentially fatal disease.

2 | PATIENTS AND METHODS

This is a single-center, retrospective chart review of all kidney transplant recipients with COVID-19 pneumonia who were admitted to the inpatient unit at the State University of New York Health Sciences University Hospital between March 18, 2020, and April 10, 2020. COVID-19 pneumonia was confirmed based on radiographic imaging coupled with real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasopharyngeal samples. Patients were excluded if they demonstrated no evidence of pneumonia. Electronic medical records were utilized to obtain demographic information including age, sex, race, year and type of transplant, cause of end-stage renal disease (ESRD), relevant comorbidities, and baseline immunosuppression regimen. We also collected last known calcineurin inhibitor levels (on admission or prior to), signs and symptoms of COVID-19 infection, and duration of symptoms prior to presentation. Baseline laboratory values including serum sodium, serum creatinine, albumin, alkaline phosphatase, aspartate transaminase, alanine transaminase, brain natriuretic peptide, creatine kinase, white blood cell count, absolute neutrophil count, and absolute lymphocyte count were recorded. If present, inflammatory markers including lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and D-dimer were collected. Microbiological data including respiratory viral panel, urine cultures, and blood cultures were collected. Patient clinical courses during admission and dispositions were recorded.

At baseline prior to admission, all patients were taking a calcineurin inhibitor and prednisone, with or without mycophenolate mofetil. Upon diagnosis of COVID-19 pneumonia, calcineurin inhibitors and antimetabolites were held for the duration of hospitalization and prednisone 5 mg was continued. All patients received hydroxychloroquine 400 mg every 12 hours for 1 day, then 200 mg every 12 hours on days 2 through 5, and azithromycin 500 mg on day 1, then 250 mg on days 2 through 5. For patients who received methylprednisolone, it was administered at a cumulative dose of 40-455 mg based on the treating provider's discretion and patients' clinical status of progressively worsening dyspnea. No additional empiric antibiotics, tocilizumab, sarilumab, or therapeutic anticoagulation was administered. At discharge, patients were instructed to continue to withhold immunosuppression until outpatient clinic follow-up, usually 3-5 days after discharge.

3 | RESULTS

3.1 | Baseline characteristics

A total of 30 kidney transplant recipients were included in our cohort. All patients were diagnosed with COVID-19 pneumonia based on bilateral patchy infiltrates shown on radiographic imaging; majority (93%) had a positive COVID-19 RT-PCR. Baseline patient characteristics are shown in Table 1. The mean age was 56 years. Nearly three-fourths of patients were of African descent, with slight male preponderance. Most common baseline comorbidities included hypertension (97%) and diabetes mellitus (47%). No patients had asthma or chronic obstructive pulmonary disease at baseline. More than half of patients were recipients of deceased donor kidney transplants; median time since transplant was 7 years. The predominant immunosuppression regimen consisted of tacrolimus and prednisone.

Upon presentation, fever, defined as a single oral temperature >100°F, was present in most patients (73%). General malaise and

TABLE 1 Baseline demographics and clinical characteristics

Baseline characteristics	N = 30
Mean age in years, n ± SD	56 ± 12
Male, n (%)	16 (53%)
Race, n (%)	
African descent	22 (73%)
Hispanic	5 (17%)
Caucasian	2 (7%)
Asian	1 (3%)
Body mass index, mean (SD)—kg/m^2	28.7 (6.9)
Years since transplant, median [IQR]	7 [4-14]
Types of transplant, n (%)	
Deceased donor	18 (60%)
Living donor	12 (40%)
Causes of ESRD, n (%)	
Hypertension	13 (43%)
Diabetes	11 (36%)
Human immunodeficiency virus	2 (7%)
Polycystic kidney disease	2 (7%)
Systemic lupus erythematosus	2 (7%)
Comorbidities, n (%)	
Hypertension	29 (97%)
Diabetes	14 (47%)
Vascular diseases	11 (37%)
Obesity	10 (33%)
Baseline immunosuppression, n (%)	
Tacrolimus	26 (87%)
Cyclosporine	3 (10%)
Mycophenolate mofetil	12 (40%)
Prednisone	30 (100%)
Last known FK506 level at admission, mean (SD)—ng/mL	7.0 (5.6)
Renal function	
Baseline creatinine, median [IQR]—mg/L	1.3 [1.0-1.8]
Baseline eGFR, median [IQR]—mL/min/1.73 m^2	57 [45-60]
CKD stage, n (%)	
2	13 (43%)
3	14 (47%)
4	1 (3%)
5	2 (7%)

respiratory symptoms such as cough or shortness of breath were common (72% and 67%, respectively). Forty-three percent of patients experienced gastrointestinal symptoms (primarily diarrhea); altered mental status was present in 20% of patients. The median duration of symptoms prior to presentation was 4 days (range 1-7 days). As compared to the baseline eGFR of 57 mL/min/1.73 m^2, admission eGFR decreased to 40 mL/min/1.73 m^2. Acute kidney injury (AKI), defined by a serum creatinine concentration increase greater than 0.3 mg/L per Kidney Disease Improving Global Outcomes (KDIGO) definition, was noted in 77% of patients. Other notable laboratory abnormalities were hyponatremia and lymphopenia compared to normal baseline values. Leukocytosis was uncommon. Inflammatory markers, including LDH, CRP, ferritin, D-dimer, and ESR that are commonly elevated in the general population, were also elevated in this transplant cohort (Table 2). Ninety percent of patients required oxygen supplementation during admission. Urine and blood cultures were negative in all patients except two patients who were critically ill on mechanical ventilation, received appropriate antibiotic treatment for positive blood cultures, and expired shortly afterward due to respiratory failure.

3.2 | Clinical outcomes

Of the 30 patients included in this cohort, seven patients required mechanical ventilation but none were extubated successfully; 23 patients have been discharged home in stable clinical condition, three of which required home oxygen. Among the seven patients who required mechanical ventilation, two were intubated en route to or in the emergency department, and five required intubation on average 3.4 days after admission; six patients expired on average 2.8 days after intubation due to respiratory failure, and one remains intubated. The overall mortality rate was 20%.

Four patients experienced acute kidney injury requiring renal replacement therapy during admission, two of which were chronic kidney disease (CKD) stage 5 at baseline, one was CKD stage 3, and one was

TABLE 2 Laboratory values upon admission, median [IQR]

Sodium—mEq/L	134 [131-137]
Creatinine—mg/L	1.8 [1.4-2.7]
eGFR—mL/min/1.73 m^2	40 [28-49]
Albumin—g/L	3.7 [3.4-4.1]
Alkaline phosphatase—units/L	70 [58-87]
Aspartate transaminase—units/L	25 [19-42]
Alanine transaminase—units/L	17 [11-22]
Lactate dehydrogenase—units/L	294 [238-427]
C-reactive protein—mg/L	76 [44-147]
Erythrocyte sedimentation rate—mm/hour	71.5 [58-80]
Ferritin—µg/L	979 [422-1977]
D-dimer—µg/mL	2900 [1053-5142]
Brain natriuretic peptide—ng/L	111 [35-380]
Creatine kinase—units/L	106 [89-461]
White blood cell count—10^3 cell/mm^3	6.7 [4.6-9.0]
Absolute neutrophil count—10^3 cells/mm^3	4.9 [3.3-6.3]
Absolute lymphocyte count—10^3 cells/mm^3	0.7 [0.5-1.0]
Neutrophil to lymphocyte ratio	7 [5-10]
Procalcitonin—ng/mL	0.2 [0.1-1.3]

CKD stage 2 and is currently intubated. Two cases of ischemic stroke occurred in our patient cohort; one was present on admission; the other patient developed ischemic stroke on sequential compression device only. Repeat viral RT-PCR was performed on several patients, and all returned positive at as far as 21 days after symptom onset; we elected not to retest patients for negative PCR but instructed them to self-quarantine for minimum 14 days at discharge. Patients were followed up in the outpatient clinic 3-5 days after discharge without issues, at which point immunosuppression was resumed. Among discharged patients, their average length of stay was 9 days.

4 | DISCUSSION

Presently, global mortality from COVID-19 is reported at 4.7%, ranging widely from 0.7% to 10.8% by location and population.[8] Despite an increasing body of literature describing clinical presentations of COVID-19 in the general population, reports on transplant recipients have been limited to case series. Our experience has shown that immunocompromised patients have similar clinical presentation compared to the general population. All patients received hydroxychloroquine and azithromycin, although clinical benefit is unclear as some patients deteriorated despite completing a 5-day course of treatment. To our knowledge, this is the largest descriptive study of a multi-ethnic cohort of kidney transplant recipients with COVID-19 pneumonia, managed with a unanimous approach of withholding calcineurin inhibitors and antimetabolites. Description of our cohort with homogenous management reduces the ambivalence in interpretation of patient outcomes, allowing readers to appreciate direct impact of interventions on patient outcomes.

In comparison with recently published case series in transplant patients, our cohort shows similar but not higher case mortality. Not only that all patients were diagnosed with COVID-19 pneumonia based on bilateral patchy infiltrates on radiographic imaging, but the highly prevalent baseline comorbidities such as hypertension, diabetes, vascular diseases, and obesity in our cohort have contributed to the 20% case mortality due to inability to overcome COVID-19 pneumonia.

4.1 | Immune response and immunosuppression reduction in COVID-19 pneumonia

Management of immunosuppression in COVID-19 infections has generated significant controversies in the transplant community due to the uncertain effects of immunosuppression on host viral defense and inflammatory response. Our center experience of withholding calcineurin inhibitors and antimetabolite during the inpatient management of COVID-19 pneumonia did not increase the risk of allograft rejection in the 30 patients included in this cohort. Profound lymphopenia—a drastic decrease in absolute lymphocyte count on admission compared to normal baseline values—was noted in most patients and suggests minimal risk of acute rejection, evidenced by the commonly adopted practice of absolute lymphocyte count monitoring as an effective marker for therapeutic response to antithymocyte globulin during induction for transplant.[9-12]

Although the exact pathogenesis of COVID-19 remains to be elucidated, the innate immune system has been widely accepted as a crucial player in the initial stages of infection. Combined with prototypical type I interferons (IFN) produced by any virally infected cells, IFN-gamma is produced by activated T-lymphocytes, stimulating innate macrophage-mediated immunity as the first line of defense against viral infections.[13,14] Although the traditional understanding of tacrolimus mechanism of action is inhibition of IL-2 transcription by $CD4^+$ T-helper cells, recent studies have shown that tacrolimus also reduces T-cell polyfunctionality, including the transcription of tumor necrosis factor (TNF) and IFN, which is crucial in antiviral activities.[15,16] T-cell exhaustion is another clinically relevant concept in the management of severe COVID-19 infections.[17-19] In a functional adaptive immune response, once the naïve T cells are activated by innate immune cells, they undergo clonal expansion and differentiation into effector $CD4^+$ and $CD8^+$ T cells that are highly functional in the elimination of virus-infected cells and the production of antigen-specific antibodies. In COVID-19 patients with severe infections, dysregulation and exhaustion of T-lymphocytes, namely decrease in number and functionality of T-helper cells, have been described as COVID-19 may mainly act on T-lymphocytes.[20] A retrospective study of patients who recovered from severe acute respiratory syndrome (SARS) demonstrated that patients who survived had high chemokine levels plus robust anti-SARS spike antibody gene expression; those who succumbed had persistent high chemokine levels but deficient adaptive immune response, suggesting that malfunction of the switch from innate to adaptive immunity contributed to fatal outcomes.[21] As current evidence strongly indicates that T-helper cells are key to successful control of SARS-CoV and Middle East respiratory syndrome-related coronavirus (MERS-CoV), and probably true for SARS-CoV-2 as well, continuation of immunosuppression such as calcineurin inhibitors and antimetabolites may exert harm in the management of this potentially fatal viral pneumonia.[14,22]

Counter-intuitively, immunosuppression has been proposed as a therapeutic option or "protective factor" by tampering the immune response that contributes to hyperinflammatory injury to the lungs from elevated cytokines.[4,23] The COVID-19 pandemic has being referred to as a gerolavic (from Greek, géros "old man" and epilavís, "harmful") infection because of substantially higher infection rates, severity, and lethality in the elderly population known to have immunosenescence.[24] If a suppressed or senescent immune system is "protective" from inflammatory injury, one would argue that the elderly population should be less susceptible to COVID-related mortality, contrary to reality. Similarly, our results have shown that while all patients were taking immunosuppression prior to admission, their COVID infections uniformly advanced to moderate-to-severe disease with confirmed diagnosis of pneumonia, while seven of the 30 patients required intubation and 20% died, cautioning the use of immunosuppression especially during the earlier phase of infection

when viral suppression by the immune system is key to halt disease progression. Direct cytopathic changes of alveolar cells by the virus have also been reported, suggesting injury etiology beyond inflammation alone.[25,26]

The use of high-dose corticosteroids warrants individualized assessment. In our cohort, 40% patients did not receive any methylprednisolone and continued low-dose prednisone only, while the rest received methylprednisolone doses ranging between 40 mg and 455 mg. The decision to use high-dose methylprednisolone (40-125 mg per dose, given per daily assessment) was based on significantly elevated inflammatory markers as well as worsening radiographic imaging. In several patients, significant improvement in previously worsening chest X-ray was observed after receiving cumulative doses of methylprednisolone 250-375 mg, while other patients continued disease progression, seemingly due to the already established advanced pneumonia, for which no interventions appeared effective. While we attempted to describe our usage of corticosteroids in COVID-19 pneumonia, we acknowledge that the practice was based on little evidence. It remains unclear which patients would benefit most from steroids and when to initiate steroids in those who rapidly progressed, due to unclear association between response to steroids, timing of steroids, baseline laboratory values, and stage of disease progression.

4.2 | Management of allograft dysfunction

Hypotension, hyponatremia, and rising serum creatinine were noted to be the most common initial presentation related to allograft dysfunction; AKI was common. Dehydration due to diarrhea, decreased oral intake, and increased insensible losses from the viral infection was the most common cause for hypovolemic hyponatremia; hypotension also contributed to AKI due to decreased autoregulation in renal allograft. Continuous intravenous infusion of normal saline was administered to all patients until volume status was normalized, and serum creatinine decreased noticeably. Despite the widely debated topic of continuing versus stopping rennin-angiotensin-aldosterone system (RAAS) inhibitors in COVID-19 infections, hypotension precluded the use of these agents.

In the general population, various pathways for kidney damage were proposed in COVID-related AKI, including cytokine damage, direct cytopathic effect, lung-kidney crosstalk, and systemic effects.[27,28] Although these factors can certainly exert negative effects on allograft function as pneumonia progresses in advanced stages, when AKI is present on admission, majority is reversible with fluid resuscitation. Resolution of AKI was associated with recovery of COVID-19.

In this rapidly evolving pandemic, transplant specialists are faced with a unique challenge to provide best care possible despite little proven evidence on management strategies. Our descriptive study provides insights on clinical outcomes of this virulent infection with homogenous withdrawal of calcineurin inhibitors and antimetabolites, showing comparable a mortality rate in an ethnic population known to have greater disease burden and mortality, without increasing the risk of acute allograft rejection.

Our study has important limitations. The sample size of 30 patients and the short duration of follow-up limit our ability to draw conclusions on the long-term impact of COVID-19 on pulmonary and renal functions, the effect of immunosuppression withdrawal on allograft function after recovery from pneumonia, seroconversion of COVID-19 immunity, and effect of COVID-19 on further risk of allograft rejection. Long-term studies are warranted to establish follow-up care of kidney transplant recipients with COVID-19 pneumonia.

5 | CONCLUSION

COVID-19 pneumonia in immunosuppressed recipients carries high mortality. No treatment modalities to date have proven noticeable antiviral benefit. Withdrawal of calcineurin inhibitors and antimetabolites, coupled with supportive measures, resulted in a case mortality rate of 20% without increasing risk of acute allograft rejection. Close follow-up of patients who recovered from COVID-19 pneumonia is warranted to monitor renal allograft function and reduce risk of rejection after viral infections.

ACKNOWLEDGEMENTS

The authors of this study would like to thank the many healthcare professionals who have devoted to providing best possible care for all patients during the COVID-19 pandemic.

CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interests to disclose.

AUTHORS CONTRIBUTIONS

TYC is responsible for the conception, development of methodology, data collection and analysis, writing, review, and revision of this manuscript. SF and SC contributed to data collection, analysis, writing, and revision of this manuscript. LLT and JHS contributed to review and revision of manuscript. RR contributed to data collection and writing of this manuscript. MR contributed to approval of institutional review board for exempt review. NS is responsible for review and revision of this manuscript.

ORCID

Tracy Yixin Chen https://orcid.org/0000-0001-7678-5332
Sara Farghaly https://orcid.org/0000-0002-8816-9454
Samantha Cham https://orcid.org/0000-0003-2860-727X
Luis Lantigua Tatem https://orcid.org/0000-0002-9351-4443
Jonathan H. Sin https://orcid.org/0000-0003-3155-6039
Roberto Rauda https://orcid.org/0000-0003-4924-7496
Maria Ribisi https://orcid.org/0000-0002-3693-2219
Nabil Sumrani https://orcid.org/0000-0001-7704-9847

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How to cite this article: Chen TY, Farghaly S, Cham S, et al. COVID-19 pneumonia in kidney transplant recipients: Focus on immunosuppression management. *Transpl Infect Dis*. 2020;22:e13378. https://doi.org/10.1111/tid.13378