Favorable outcome of COVID-19 among African American (AA) renal transplant recipients in Detroit

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Abstract
Transplant recipients are vulnerable to infections, including COVID-19, given their comorbidities and chronic immunosuppression. In this study, all hospitalized renal transplant recipients (RTR) with a positive nasal swab for Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV2) seen consecutively between 03/01/2020 and 05/01/2020 at the Detroit Medical Center were included. Data on demographics, clinical presentation, laboratory findings, management, and outcomes were collected. Twenty-five patients were included, all African American (AA) and deceased-donor transplant recipients. The most common presenting symptom was dyspnea, followed by fever, cough and diarrhea. Multifocal opacities on initial chest x-ray were seen in 52% patients and 44% of patients had a presenting oxygen saturation of less than or equal to 94%. Four patients (16%) required transfer to the intensive care unit, one required intubation and one expired. COVID-19-infected RTR in this cohort had low mortality of 4% (n = 1). Despite multiple comorbidities and chronic immunosuppression, our cohort of African American RTR had favorable outcomes compared to other reports on COVID-19 in RTR.

Keywords
infection and infectious agents, kidney disease: infectious, lung disease: infectious, viral

1 | INTRODUCTION

As of September 13th 2020, coronavirus disease (COVID-19) had affected over 28 million individuals worldwide and the majority of cases were detected in the United States.1 The Centers for Disease Control (CDC) report a mortality of about 6% in the United States.2 By May 1, 2020, there were 46,072 patients with COVID-19 in the state of Michigan, with a case fatality rate of 9.4%, making Detroit one of the epicenters of the disease.3 Patients over the age of 65 years and those with underlying conditions including chronic lung or heart disease are at risk for severe infection and high mortality. Likewise, patients with underlying chronic immunosuppression are also at risk for poor outcome.4 Furthermore, disparities in COVID-19 outcomes among racial and ethnic minorities including AA are well recognized.5,6 There have been several published cases series in solid organ transplant recipients, including renal transplant, which confirm suboptimal outcome in this population.7-15 We present data on 25 SARS-CoV-2-infected AA renal transplant recipients (RTR) in a single center located in the City of Detroit, with excellent outcome.
2 | METHODS

We included patients who had undergone kidney transplantation and were hospitalized at the Detroit Medical Center's (DMC) Harper University Hospital (HUH) with a positive SARS-CoV-2 RT-PCR test. Persons under investigation (PUI) with a negative test were not included. Eligibility for hospital admission was determined by emergency room physicians and criteria included hypotension (requiring resuscitation or withholding antihypertensive drugs), oxygen desaturation (≤ 93% O₂ sat on room air or requiring increased supplemental oxygen from baseline), fever, abnormal chest X-ray, and evidence of acute kidney injury.

All data were collected from the patients’ electronic medical record (EMR) as a retrospective chart review. The time frame of testing was from 3/1/2020 through 5/1/2020, which includes the peak period of COVID-19 in the State of Michigan. Testing was done at the DMC University laboratories, and consisted solely of reverse-transcriptase polymerase chain reaction (RT-PCR) via specimens obtained from nasopharyngeal swabs. Institutional review board approval for this retrospective study was granted by both Wayne State University (WSU) and the DMC.

Information collected included the following: patient’s age, gender, comorbidities, date of transplantation, race, type of transplant donor (deceased or living), induction and maintenance immunosuppression, date of COVID 19 infection, symptoms, laboratory findings, need for hospitalization or admission to intensive care unit, need for intubation, treatment and outcome.

3 | RESULTS

Of the 340 renal transplant recipients who are mostly AA (over 85%) followed at our center, twenty-five RTR were diagnosed with COVID-19 during the study period. All 25 met criteria for hospitalization and none were discharged from the Emergency Department (Table 1). The 25 RTR had a median age of 56 years (interquartile range; IQR, 47–66). All were African American and deceased-donor transplant recipients. Fourteen (56%) were men and 11 (44%) were women. Three patients were within 6 months of receiving a kidney transplant. The median time since transplant to diagnosis of COVID-19 infection, symptoms, laboratory findings, need for hospitalization or admission to intensive care unit, need for intubation, treatment and outcome.

| TABLE 1 Demographics and clinical presentation |
|-----------------------------------------------|
| Baseline demographics, n (%) or median (IQR)  |
| All patients (n = 25)                          |
| Age, years                                    | 56 (47–66) |
| Male gender                                   | 14 (56)    |
| African American                              | 25 (100)   |
| Time since transplant, months                 | 78 (35–121) |
| BMI, kg/m²                                    | 29.5 (26–39) |
| Time on dialysis, months                      | 47 (34–69) |
| Baseline comorbidities, n (%)                 |            |
| Hypertension                                  | 24 (96)    |
| Diabetes                                      | 13 (52)    |
| Cardiovascular disease                        | 11 (44)    |
| Pulmonary disease                             | 10 (40)    |
| Smoking history                               | 8 (32)     |
| Cancer                                        | 3 (12)     |
| Maintenance immunosuppression, n (%)          |            |
| Tac/MPA/prednisone                            | 20 (80)    |
| Tac/prednisone                                | 3 (12)     |
| Tac/MPA                                       | 2 (8)      |
| Clinical presentation, n (%) or median (IQR)  |
| Shortness of breath                            | 16 (64)    |
| Cough                                         | 14 (56)    |
| Diarrhea                                      | 14 (56)    |
| Fever (temperature > 38.4°C)                  | 14 (56)    |
| Fatigue                                       | 11 (44)    |
| Chills                                        | 7 (28)     |
| Myalgia/arthritis                             | 6 (24)     |
| Nasal congestion                              | 3 (12)     |
| Nausea/vomiting                               | 3 (12)     |
| Percent oxygen saturation                     | 95 (90–98) |
| Abnormal chest imaging                        | 16 (64)    |
| Laboratory values, median (IQR)               |
| Tacrolimus trough, ng/mL                      | 7.2 (6.5–8.7) |
| White blood cell count, per mm²               | 5500 (4300–7000) |
| Absolute lymphocyte count, per mm²            | 900 (600–1100) |
| ANC/ALC                                       | 5.2 (4.0–7.3) |
| Serum creatinine, mg/dL                       | 1.9 (1.5–3.2) |
| Serum ferritin, ng/mL                         | 1275 (371–2293) |
| D-dimer, mg/L                                 | 2.0 (1.0–5.0) |
| C-reactive protein, mg/L                      | 79 (48–157) |

Note: Data reported in median (interquartile range; IQR), or n (%). Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; MPA, mycophenolic acid; Tac, tacrolimus.
had a history of hypertension (n = 24, 96%), thirteen patients (52%) with diabetes, eleven (44%) patients had cardiovascular disease, ten (40%) had pulmonary disease, and three (12%) had a preexisting history of malignancy. Only five (20%) patients had a body mass index (BMI) within normal range, 5 (20%) were overweight, and 15 (60%) were obese. Fifteen (60%) patients reported they had never smoked, 7 (28%) reported previous history of smoking, and 1 (4%) reported current tobacco use.

Reported symptom onset ranged from 1 day to 2 weeks before admission. The most common presenting symptom was shortness of breath in 16 (64%) patients, and diarrhea in 14 (56%). Cough and fever also were reported in 14 (56%) patients, and fatigue in 11 patients.

About half of the patients had bilateral/multifocal opacities noted on initial chest x-ray (n = 13, 52%), whereas three (12%) had unilateral opacities and 8 (32%) had unremarkable radiographs initially. Eleven patients (44%) had oxygen saturation less than or equal to 94%, ten (40%) required oxygen supplementation at presentation. Median values for laboratory results obtained at the time of presentation included white blood cell count 5300/mm² (IQR, 4300–7000) and absolute lymphocyte count 900/mm² (IQR, 600–1100). We observed high levels of inflammatory markers, serum ferritin (1275 ng/mL, IQR 371–2293), and C-reactive protein (79 mg/L; IQR 48–175).

Immunosuppression management during hospitalization consisted of dual therapy with tacrolimus and maintenance prednisone. The median tacrolimus trough at presentation was 7.2 ng/mL (IQR 6.5–8.7) and adjusted as necessary to maintain the target trough per center protocol (up to 6 months, 8–10 ng/mL; 6 months–24 months, 6–8 ng/mL; > 24 months, 5–7 ng/mL). Treatment with mycophenolic acid was withheld at presentation. Hospital guidelines for COVID-19-specific adjuvant therapy varied as the pandemic evolved (Table 2). Initially, the guidelines recommended hydroxychloroquine to all patients who were admitted and at risk for severe disease, which included all RTR. Those who met the criteria received 400mg twice daily on day 1, followed by once daily for 4 additional days. Later, the guidelines also included oral or IV steroids for patients with sp02 < 93%, requiring >6L/min of oxygen, ferritin > 1000 ng/mL, or doubling of ferritin within 24 hours. Those who qualified for high-dose steroids received approximately 1mg/kg/day for 3 days. In our series, 8 patients (32%) received hydroxychloroquine alone and 12 patients (48%) received a combination of hydroxychloroquine and steroids.

Over the course of hospitalization, sixteen patients (64%) required oxygen therapy with nasal cannula, high flow oxygen, or mechanical ventilation. Eight patients (33%) developed hypotension requiring resuscitation or withholding antihypertensive medications. Four patients (12%) required admission to intensive care unit, of whom one (4%) died. Death occurred in a 73-year-old woman with a history of diabetes, hypertension, and coronary artery disease. Acute kidney injury, defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria, was observed in 64% (n = 16) patients. All RTR recovered to near baseline allograft function.

Two patients were readmitted. One patient had non-COVID-19-related nephrotic syndrome nine days after discharge and presented with fluid retention that resolved with diuresis. The second patient was readmitted within one week of discharge for ongoing COVID-19-related dyspnea and was discharged on supplemental oxygen, which has since been weaned. Seven patients (29%) were discharged with supplemental home oxygen. Two patients had confirmed bacterial coinfection (methicillin-resistant Staphylococcus aureus bacteremia and Enterococcus sp urinary tract infection), one had presumed hospital-acquired pneumonia with negative culture data. All of the recovered patients have been followed after discharge for a median time of 45 days and have made full symptomatic recovery. Antiproliferative agent, mycophenolate mofetil, was reintroduced 3–4 weeks after discharge based on resolution of symptoms and stable laboratory parameters.

## TABLE 2 Management and outcomes

| Management, n (%) | All patients (n = 25) |
|------------------|----------------------|
| Hydroxychloroquine + high dose corticosteroids | 12 (48) |
| Hydroxychloroquine alone | 8 (32) |
| High dose corticosteroids alone | 1 (4) |
| Outcome, n (%) or median (IQR) |         |
| Acute kidney injury | 16 (64) |
| Hospitalized | 24 (96) |
| ICU admission | 4 (16) |
| Readmission for COVID-19 | 2 (8) |
| Intubated | 1 (4) |
| Died | 1 (4) |
| Discharged with supplemental oxygen (n = 24 patients admitted) | 7 (29) |
| Length of stay, days, median (IQR) | 5.5 (4-9.5) |

### 4 DISCUSSION

We report favorable outcome of COVID-19 in twenty-five deceased-donor RTR. Our 4% (n = 1) mortality is markedly lower than what other renal transplant series have reported. There was no selection bias in the study as all COVID-positive transplant recipients seen in the emergency room during the study period met criteria for hospitalization, thus no COVID-19 positive patients were excluded. Data from New York renal transplant recipients with COVID-19 have shown mortality ranging from 13% to 28%. In Europe, mortality in this population has been similar between 9% and 25%. It is important to mention that we only included patients with confirmed COVID-19 infection, and asymptomatic patients were not screened. The majority of patients had initial radiographic findings of pneumonia (64%) compatible with COVID-19 infection, and 44% had oxygen saturation at presentation of less than or equal to 94% qualifying as severe illness per current Infectious Diseases Society of America (IDSA) treatment guidelines. During the course of hospitalization,
64% of cases required further measures such as oxygen supplementation or mechanical ventilation.

Many of our patients presented with atypical symptoms including diarrhea in addition to upper respiratory symptoms. This is in contrast to other case series in RTR where diarrhea was less frequent. A recent large registry study comparing respiratory and gastrointestinal phenotypes in COVID-19 RTR found patients with gastrointestinal symptoms had more favorable outcomes as opposed to those with isolated pneumonia.

This is the first published case series reporting outcomes in a group comprised solely of African American RTR with COVID-19. In Michigan, AA make up 14.1% of the state population; however, they comprised 30% of the confirmed COVID-19 cases and approximately 40% of case fatalities. This disproportionality is being attributed to socioeconomic and health disparities such as cardiovascular disease, diabetes, and kidney disease. These comorbidities contribute to more severe COVID-19 disease course and increased risk of death. In another COVID-19 study from Detroit with > 70% AA, 20% died within 30 days. Male sex and age > 60 years were associated with mortality, while AA race was not. Comorbidities were similar in this study as in our cohort. Remarkably, our transplant cohort, despite the presence of comorbidities and risk factors, had an excellent outcome.

Recent studies suggest that non-white, socioeconomically disadvantaged and non-English speaking populations carry disproportionate COVID-19 burdens. In a study of 2595 patients at a Milwaukee Hospital, AA patients (59.1%) were 5.4 times more likely than those of other races to test positive. However, increased likelihood of death was associated with shortness of breath on admission, high BMI and age older than 60 years, but was not linked to race or socioeconomic status. The authors speculated that high numbers of infections in AA patients may be attributable to crowded housing and fewer work-from-home options. No inherent racial vulnerability to adverse coronavirus outcomes was noted. In a Pediatric study of 1000 patients in Washington, DC, minority children were 2-3 times more likely than white children to have COVID-19. AA children and those of other racial groups were more likely than white children to report known coronavirus exposures (34.9% of AA vs. 11.3% of whites). In contrast, a study from New York city found similar outcomes among 5902 COVID-19-infected AA and Hispanics and whites. They explained that accessibility to services in comprehensive health care environment may attenuate, if not eliminate, racial/ethnic differences in COVID-19 mortality rates. Finally, Khazanchi et al, in a communication in JAMA, argued that racism rather than race may explain COVID-19-associated racial health inequities. They wrote, "...rather than validating long-debunked hypotheses about intrinsic biologic susceptibilities among non-white racial groups, the evidence to date reaffirms that structural racism is a critical driving force behind COVID-19 disparities".

Case reports in the general population have noted high levels of markers of inflammation with severe manifestation of COVID-19. Although our cohort included patients with elevated D-dimer, ferritin, and CRP, it did not necessarily portend poor outcomes as seen in other reports of RTR.

In this case series, therapy with calcineurin inhibitors was maintained at target troughs without tapering for severity of disease or acute kidney injury. In vitro studies have shown that SARS-CoV may enhance calcineurin-dependent dephosphorylation of NF-AT to trigger cytokine generation. Therefore, blocking NF-AT signaling pathway with calcineurin inhibitors may have an inhibitory effect on immune cell activation and consequent cytokine dysregulation, seen in severe SARS-CoV infection. In addition, in vitro studies have shown calcineurin inhibitors to decrease SARS-CoV replication. Possibly, use of such drugs may lead to reduced severity of "cytokine storm," hence improving disease outcome.

In June 2020, the IDSA guidelines were updated to include the use of glucocorticoids among hospitalized patients with severe COVID-19. A recent study showed that an early course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes. Preliminary results from the RECOVERY trial report that the use of dexamethasone reduced 28-day mortality among patients receiving invasive mechanical ventilation or oxygen supplementation. Use of steroids in our patients likely contributed to a good outcome.

Limitations of this study include the relatively small number of patients, its retrospective nature and short follow-up. In addition, asymptomatic patients or those suspected with COVID-19 were not included.

5 | CONCLUSION

Prognosis was excellent in our consecutive cohort of 25 hospitalized AA RTR with COVID-19 admitted during the height of the pandemic. Most patients, despite risk factors for poor outcome, gradually improved and made full recovery. Use of corticosteroids and perhaps maintaining optimal levels of calcineurin inhibitor may have contributed to a muted adverse host inflammatory response and hence, an improved outcome. More data are needed regarding the role of calcineurin inhibitors during COVID-19 infection, particularly in the AA population.

CONFLICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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