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ORIGINAL ARTICLE

Outpatient COVID-19 surveillance testing in orthotopic heart transplant recipients

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Abstract

COVID-19 case fatality rate in the United States is currently reported at 4.8% based on the confirmed cases of COVID-19. However, there are conflicting reports of estimated deaths in the post-cardiac transplantation patient population associated with COVID-19.

Methods: Observational, retrospective analysis of a large cohort of post Orthotopic Heart Transplantation (OHT) patients in a high volume heart transplantation program in Dallas, Texas underwent outpatient COVID-19 screening and testing for both SARS-CoV-2 nasopharyngeal RT-PCR and anti-SARS-CoV2 IgG serology as a result of a clinic protocol to facilitate re-opening of face-to-face outpatient clinical visits.

Results: The full outpatient cohort tested at time of their clinic visit tested negative for COVID-19 by nasopharyngeal RT-PCR. Only 2 patients tested seropositive for anti-SARS-COV2 IgG. Five positive inpatient cases were also identified and all, but one recovered.

Conclusion: A COVID-19 surveillance protocol can be easily instituted in this high-risk population and facilitate safe transplant clinic operation. As the cases and prevalence increase across the United States, further strategies will need to be developed to determine the best course of action to help manage this select population while minimizing their exposure to the ongoing pandemic.

KEYWORDS
cardiac transplantation, clinical decision-making, complication: infectious, infection and infectious agents, risk assessment/risk stratification, viral

1 | INTRODUCTION

The viral and host responses to the novel coronavirus, SARS-CoV-2, result in a spectrum of presentation ranging from minimally symptomatic individuals to the severe acute respiratory syndrome, COVID-19. To date, COVID-19 has affected over 9 million people worldwide, with over 2 million cases reported in the United States alone. Relative risk of morbidity and mortality from COVID-19 rises with each passing decade of age and patients with co-morbidities including hypertension, diabetes mellitus, obesity, and other chronic co-morbid conditions.[1]

Case fatality rate in the United States is currently estimated at 4.8% based on the confirmed cases of COVID-19.[2] However, there are mixed estimates of deaths in the post-cardiac transplantation patient population associated with COVID-19. As per the C19Txr.org registry (accessed 7/22/2020), there have been only 5 post- OHT

deaths with 17 patients undergoing treatment and 25 patients that have been reported as fully recovered. Conversely, Latif et al (2020) describe a 28 post OHT patient case series with confirmed COVID-19 infection resulting in a high case fatality rate of 25%, which is higher than other reported at-risk patient cohorts.[3] Immunocompromised patients, specifically OHT recipients, are hypothesized to represent a high-risk group. However, the prevalence and risk of COVID-19 in an asymptomatic, clinically stable, post OHT patient population, have yet to be quantified.

Our center sought to maintain active management for routine and symptom-based care in our post-cardiac transplant clinic during the onset of the pandemic. Our COVID infection or case rate in the middle of April began at approximately 18 000 cases that rapidly rose to over 103 000 by the middle of June (worldometers.info).

With the public health risk to patients and staff in mind, we instituted a standard clinical practice to ensure adequate epidemiologic surveillance to facilitate reduction in the spread of this highly contagious pathogen. Per CDC guidelines, our protocol was instituted bearing in mind the current unknown incidence and prevalence of asymptomatic and pre-symptomatic SARS-CoV-2 viral RNA and seropositivity in a group perceived to be high risk.

Herein, we describe a large cohort of post OHT patients in a high volume heart transplantation program in Dallas, Texas that underwent COVID-19 screening by both SARS-CoV-2 nasopharyngeal reverse-transcriptase polymerase chain reaction (RT-PCR) and anti-SARS-CoV2 IgG serology as a result of a clinic protocol to facilitate re-opening of face-to-face clinical encounters.

2 | METHODS

This was a retrospective, observational analysis of screened asymptomatic OHT patients that presented to our clinic after the protocol was instituted. Data were collected and approved by the Institutional Review Board (IRB) of Baylor Scott & White Research Institute under a retrospective umbrella protocol specific to COVID-19. Patients were pre-screened for symptoms via phone prior to appointment scheduling, prior to entering clinic on day of appointment, and again immediately before testing as per current CDC guidelines and triaged to outpatient drive-through testing or emergency room if warning signs present. All adult stable postOHT patients seen as per routine follow-up for an in-person outpatient visit from mid-April 2020 through mid- June 2020 were offered voluntary testing on the day of their clinic visit via this clinic protocol (Figure 1).

All patients underwent both real-time SARS-CoV-2 PCR using primers against the three WHO-consensus target sequences (using Luminex Magpix, Roche Cobas, and Thermo Fischer Taqpath) and/or SARS-CoV-2 IgG serology testing (Abbott Architect). Nasopharyngeal swab was obtained by trained nursing staff in conjunction with typical intake procedures during the clinic visit. Serology was obtained as part of routine clinic phlebotomy processes.

Demographic data including geographic area of residence in relationship to the transplant institute, age, gender, race, date of transplantation, and immunosuppression regimen were collected retrospectively. Additionally, co-morbid conditions as documented in the most recent progress notes that included hypertension, diabetes mellitus, chronic kidney disease (CKD inclusive of grade 1-5) and obesity (BMI > 30) were also abstracted. Treatment data for those patients following in our program who were admitted to our hospital or managed by the program for COVID-19 in an outpatient setting were also collected. Data were deidentified following collection.

3 | RESULTS

Our cohort consisted of 155 postOHT patients during in-person clinic visits that were tested at least once for the 2019 novel coronavirus (SARS-CoV-2) via RT-PCR and anti-SARS-COV2 IgG serostatus. All patients that presented to the clinic during this time period volunteered for testing during their clinic visit except for one. Of note, that patient that did not get tested, elected not to due to a scheduled COVID testing in prep for a surgery within 48 h after his clinic visit. Over the 3-month period, 94% of patients were only tested once (n = 148). Only 6% (n = 9) of the patients were scheduled for more than 1 clinic visit during the 3-month observation period as per clinic protocol (see Figure 1).

The average age of patients in our cohort was 62 years, and 109 (70.3%) were men. The average time from OHT to their clinic visit

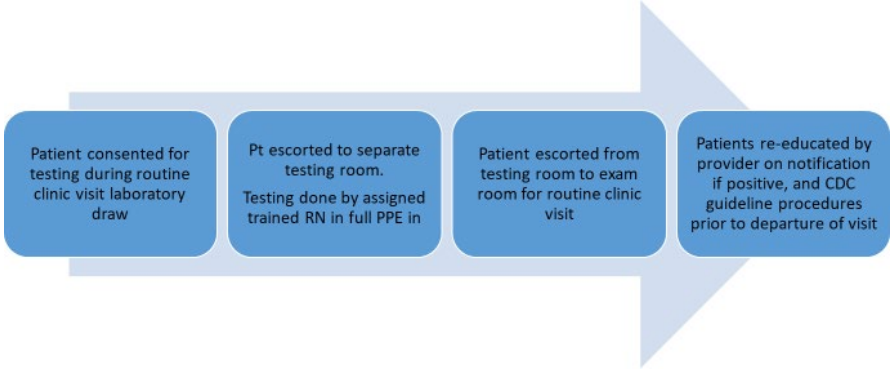

FIGURE 1 Outpatient clinic protocol for COVID 19 testing for post-cardiac transplantation patients

was 148 days. Most of our patients travelled > 30 miles distances from our transplant institute (Figure 2). Current burden of co-morbid conditions for our cohort included the following: hypertension (82%, *N* = 128), CKD (57.4%. *N* = 89) patients, DM (42.5%, *N* = 66), and obesity (43.2%, *N* = 67) (see Table 1). All patients (100%) were on immunosuppression, the standard regimen including calcineurin inhibitors, mycophenolate mofetil, and corticosteroids (per our taper protocol). Antiproliferative agents were concomitant medications for 10.3% (*N* = 15) of patients either secondary to coronary artery vasculopathy (CAV), malignancy, and/or advanced kidney disease.

The full cohort tested negative for SARS-CoV-2 by nasopharyngeal RT-PCR at time of their clinic visit. Only 2 patients tested seropositive for anti-SARS-CoV2 IgG. Of note, neither patient reported either ever having symptoms throughout this early pandemic timeline nor where they aware of being exposed to any positive tested or symptomatic person. To date, only one if these 2 patients have been re-tested for anti-SARS-CoV2 IgG. This patient remained positive 1 month post his first test. The other patient was not re-tested as her follow-up clinic visit fell outside this observation period.

One asymptomatic male patient who deferred testing during his clinic visit, 2 days thereafter, presented via his local emergency room symptomatic and tested positive. Patient was immediately transferred back to our institution with severe COVID-19 (defined by SpO2 ≤ 94% on room air with radiographic infiltrates). He received a 5-day course of remdesivir supplied via emergency use authorization and was discharged home, still seronegative 8 days after his clinic encounter, postulating early disease. Furthermore, patient has been re-tested within our healthcare system 6 times, and to date has still tested positive via nasal RT-PCR.

Additionally during the study period, a total of 5 OHT patients from our program were hospitalized for COVID-19 (one out of state, one in-state at distances prohibitive for transport, and three at our center including the case described above). All three patients treated at our institution received remdesivir, one of whom required intubation that escalated to veno-venous ECMO for progressive acute respiratory disease syndrome (ARDS). That patient is approaching nearly 1 month of ECMO support at the time of writing of this manuscript, whereas the others have fully recovered.

4 | DISCUSSION

We demonstrate the feasibility of clinic re-opening by integrating routine testing in immunosuppressed patients who are potentially asymptomatic or pre-symptomatic at the earliest phases of the viral illness. No known patients hospitalized for COVID-19 passed through our clinic while overtly infected, except for the one asymptomatic patient case who deferred testing, ultimately testing positive, requiring admission, and receiving antiviral treatment as previously described.

The absence of actively infected OHT patients in our clinic may have a multifactorial origin, including the cohort's inherent acceptance of self-masking, social distancing, and associated hygiene practices when compared to non-transplant patients. To that end, it may be geographically and program dependent. This protocol was initiated at a time when the prevalence of COVID-19 was relatively low in the general geographic area of our transplant center; however, the prevalence rose to ~10% of our hospital inpatient census during this interval, with 5 of our patient panel presenting via appropriate emergency room pathways resulting in admission due to COVID-19.

Theoretically, transplanted patients might be more susceptible to SARS-CoV-2 infection with atypical manifestations due to chronic use of immunosuppressive drugs with a corresponding risk of lymphopenia, a well-established adverse prognostic feature in COVID-19. However, paradoxically, acute immunosuppression is under active investigation as a salvage therapy for COVID-19, and tacrolimus possesses antiviral activity against coronaviridae in vitro[4-6]

There is a paucity of data to dictate any standard guideline or recommendation for surveillance testing in this patient population. Currently, the CDC offers that testing asymptomatic high-risk patients is appropriate if deemed a priority by clinicians. It does not dictate how often nor for how long. Moreover, to date there is no

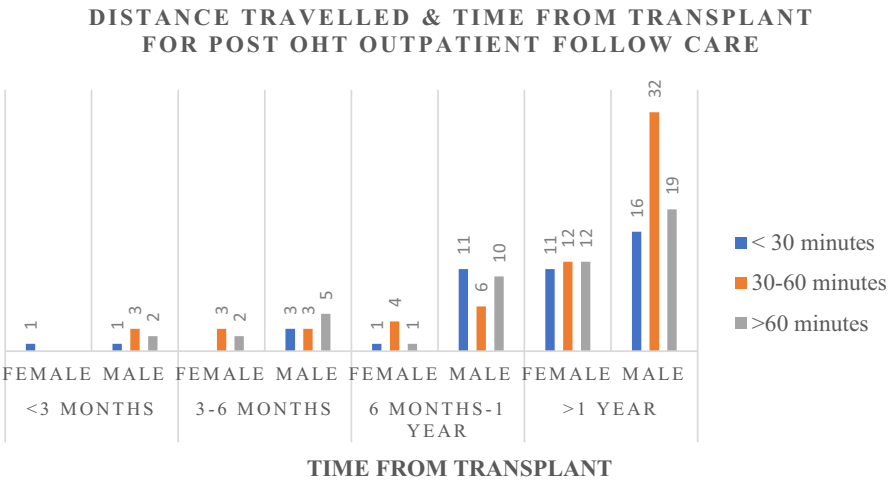

FIGURE 2 Distance travelled and time from transplant for post OHT outpatient follow care

TABLE 1 Demographics

	Total	Female	Male
N	155	46 (29.6%)	109 (70.3%)
Age at testing (years)	62 (22-80)	59 (22-78)	63 (22-80)
Race			
African American	38 (24%)	11 (7%)	27 (17%)
Asian	4 (2.5%)	1 (0.63%)	3 (2%)
Caucasian	93 (59%)	28 (17.7%)	65 (41.1%)
Hispanic/Latino	21 (13.3%)	6 (3.8%)	15 (9.5%)
Not Hispanic/ Latino	2 (1.27%)	1 (0.63%)	1 (0.65%)
Co-Morbid Conditions			
HTN	128 (82%)	34 (21%)	94 (60%)
Diabetes Mellitus (I or II)	66 (42.5%)	15 (9.67%)	51 (32.9%)
CKD (Grade 1-5)	89 (57.4%)	24 (6.45%)	65 (41.93%
BMI> 30	67 (43.2%)	21 (13.54%)	46 (29.67%)
Time from Transplant			
3–6 months	16 (10.3%)	5 (3.2%)	11 (7.1%)
6 months–1 year	33 (21.2%)	6 (3.8%)	27 (17.4%)
<3 months	7 (4.5%)	1 (0.65%)	6 (3.8%)
>1 year	99 (63.8%)	34 (21.9%)	65 (41.9%)
Distance from Center			
30–60 min	62 (40%)	19 (12.2%)	43 (27.7%)
<30 min	42 (27.1%)	12 (7.7%)	30 (19.3%)
>60 min	51 (32.9%)	15 (9.6%)	36 (23.2%)

documentation supporting that active disease in an immunocompromised patient population *does not* exist. Could or should surveillance testing in this patient population be warranted as we move toward a pre-COVID clinical routine? Postulating, would this reduce the spread to non-infected more vulnerable OHT patients, family members and clinical staff? Could this enhance more stringent surveillance/treatment strategies for those patients that test positive then symptomatically progress thus resulting in reduction in mortality?

We are still in our infancy of understanding the full weight and scope of this virus.

As anticipated, with the re-opening our communities, COVID-19 cases were dramatically rising, highlighting a need to rapidly address the safe care for recipients of solid organ transplants.

Assessments of incidence and prevalence of this patient population in our program helped to facilitate appropriate measures that allowed us to potentially intervene, and thus potentially avoid poor outcomes. The time period studied was fraught unknowns, and we recognized quickly that newly transplanted patients were frequently under-served, and at risk for poor outcomes using only tele-health medicine venues. Moreover, with the heightening patient and clinical staff anxiety, we felt this helped to set a stage for allowing more live patient visits, and live clinical staff return to a pre-COVID outpatient infrastructure in the safest manner possible. More research and appropriate guidelines to how this should be best achieved are warranted.

5 | LIMITATIONS

This trial was a retrospective, observational, and moreover a feasibility trial of a very niche high-risk patient population. As inherent in these types of trials, we recognize that this cannot be generalized to any other population due to the limited time-period observed, coupled with the earlier stages of the pandemic represented which was very specific to our patient population studied. Additionally, we recognize the significant regional variances of patient testing protocols, access to testing, and population density during this time period of the pandemic.

6 | CONCLUSION

A COVID-19 surveillance protocol can be easily instituted in an outpatient transplant clinic. As the cases and prevalence increase globally, further strategies will need to be developed to determine the best course of action to help actively manage these patients while minimizing their exposure to the ongoing pandemic. Moreover, routine testing in OHT patients who are asymptomatic, or possibly with mild symptoms, needs to be considered and assessed as we maneuver through the next phases of this pandemic.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

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

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