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COVID-19 in heart transplant patients: Case reports from Brazil

Rafaela Vale de Miranda Soriano[1] | Joao Manoel Rossi Neto[1] | Marco Aurelio Finger[1] | Carolina Casadei dos Santos[1] | Hui Tzu Lin-Wang[2]

[1]Department of Heart Transplantation, Dante Pazzanese Institute of Cardiology, São Paulo, Brazil

[2]Laboratory of Molecular Investigation in Cardiology, Dante Pazzanese Institute of Cardiology, São Paulo, Brazil

Correspondence
Rafaela Vale de Miranda Soriano, Instituto Dante Pazzanese de Cardiologia, Ambulatório de transplante Cardíaco, Av. Dr. Dante Pazzanese 500, Ibirapuera, São Paulo, Brasil.
Email: rafavaledemiranda@yahoo.com.br

Abstract

Introduction: The COVID-19 pandemic continues, with a late hyperinflammatory phase. The immunosuppressive therapy used in heart transplant patients, in theory, could reduce inflammation, thus benefitting patients with COVID-19. So far, however, there is still very little literature on this subject.

Methods: This is a single-center retrospective study. We described laboratory parameters and clinical outcomes from 11 heart transplant patients with COVID-19 assisted at Dante Pazzanese Institute of Cardiology between March and July 2020.

Results: Patients with ages of between 35 and 79 years were enrolled, and heart transplantation ranged from 3 to 264 months. The main comorbidities were diabetes mellitus (9/11; 81.8%), hypertension (10/11; 90.9%), and chronic renal disease (6/11; 54.5%). Cyclosporine A was used in 10 (90.9%) patients, mycophenolate mofetil in 9 (81.8%) patients, and mTOR inhibitor in 5 (45.5%) patients. Fever and cough were observed in 8 (72.7%) patients, and dyspnea and gastrointestinal symptoms in 5 (45.5%) patients. Lymphopenia was observed in 10 (90.9%) patients and thrombocytopenia in 5 (45.5%) patients. The higher level of troponin associated with chest tomography above 50% of bilateral pulmonary infiltrates with ground-glass opacity (GGO) was observed in those with the worst outcomes. Nine patients needed intensive care, and hospital stay ranged from 4 to 21 days, with 2 (18.2%) patients requiring vasopressor drugs and mechanical ventilation, and three (27.3%) patients dying due to COVID-19 complications.

Conclusion: Heart transplant patients had similar symptoms and outcomes as the general population; immunosuppressive therapy seems not to have protected them. Patients who presented higher levels of troponin and D-dimer, associated with greater GGO pulmonary infiltrates, had worse outcomes. More studies with larger cohorts may clarify immunosuppressive effects on COVID-19 outcomes.

KEYWORDS
COVID-19, D-dimer, heart transplantation, SARS-CoV-2, troponin

1 | INTRODUCTION

The SARS-CoV-2 is responsible for the coronavirus disease 2019 (COVID-19); the SARS-CoV-2 infection continues to spread globally with devastating results, and it is considered by the World Health Organization (WHO) as a pandemic disease.[1] COVID-19 has also been responsible for many deaths around the world, including Brazil. According to the Brazilian Health Ministry, 358 425 individuals died up to April 14, 2021, and the lethality was 2.6%.[2]

In theory, one might anticipate a higher attack rate of pneumonia, acute respiratory syndrome, and septic shock for organ transplant recipients.[3] However, immunosuppression can inhibit the secondary hyperinflammation caused by a cytokine storm, responsible for the majority of deaths from COVID-19.[4] Similarly, it can lead to atypical clinical presentations or increasing the risk of adverse events.[5] Herein, we report a single-center retrospective study from heart transplant patients with COVID-19, as a preliminary observational context to inform treatment and clinical outcomes.

2 | METHODS

2.1 | Ethical statement

This study was approved by the institutional review board of Dante Pazzanese Institute of Cardiology (protocol 4.433.303), which was conducted in accordance with Resolution 466 by the Brazilian Health Council/National Health Surveillance Agency and ICH-GCP for good clinical practices.

2.2 | Patients and demographic data

Of the 145 adult heart transplant recipients routinely followed in our institution between March and July 2020, 11 of them presented to our institution for COVID-19 care and were included in this study. After heart transplantation, all patients received a standard immunosuppressive regimen with cyclosporine at a 4 mg/kg/day dose, mycophenolate mofetil at a 1.5 g/day dose, and prednisone at a 0.4 mg/kg daily dose. Alternative immunosuppressive therapy was prescribed whenever necessary. All data, such as clinical history, laboratory results, inflammatory and radiological issues, and specific drugs used, were retrospectively collected.

The primary outcome was death caused by COVID-19; a secondary outcome was the need for intensive care unit (ICU), mechanical ventilation, along with acute renal dysfunction.

2.3 | RT-PCR for COVID-19 diagnosis

To extract SARS-CoV-2 nucleic acids from nasopharyngeal swabs, the QIAamp® Viral RNA (Cat. #52906; Qiagen, GmbH, Hilden, GY) was applied. The RT-PCR was carried out in a Rotor-Gene thermal cycler by using QuantiTect Probe RT-PCR Master Mix (Cat. # 204 443; Qiagen GmbH, Hilden, GY).

The primers used for RT-PCR analysis were recommended by the US Centers for Disease Control and Prevention,[6] commercially designed (2019-nCoV RUO Kit) by Integrated DNA Technologies, Coralville, IA, USA (www.idtdna.com), containing primers N1 and N2 specific for SARS-CoV-2 and human RNase P as positive controls. The samples were considered positive when all measured parameters (N1, N2, and RNase P) showed lower than 35 Ct (cycle threshold).

2.4 | Serology for IgG detection

Enzyme-linked immunosorbent assay (ELISA) was applied to detect IgG anti–SARS-CoV-2 protein N (GenBank: QIG56001.1) in serum of patients. The 96-well plates were firstly adsorbed with 1ug/ml of N protein, incubated overnight at 4°C, blocked with 1% bovine serum albumin diluted in PBS buffer for 1h at 37°C, and then incubated with the serum (dilution 1/100) for 2 h at 37°C. The HRP anti-human IgG secondary antibody (Sigma, USA) at 1:30 000 of dilution was added and incubated at 37°C for 1 h. The TMB substrate (Thermo Scientific, USA) was added to each well and stopped with 1N HCl after 3 min of incubation. The absorbance was read at 450 nm. The cutoff value assumed was 0.450 AU.

3 | RESULTS

The age of patients enrolled was between 35 and 79 years. The main comorbidities were diabetes mellitus (9/11; 80%), hypertension (10/11; 90%), and chronic renal disease (6/11; 54%). Heart transplantation ranged from 3 to 264 months. Cyclosporine A was used in 10 (90%) patients, mTOR inhibitor in 45% (5/11) patients, and mycophenolate in 80% (9/11) patients. Immunosuppression was discontinued in two patients: One had septic shock and the other had severe leukopenia (270/mm^3), and both died. Common symptoms at onset of illness were fever and cough in 72% of cases, and dyspnea and gastrointestinal symptoms in 45% of cases (Table 1).

Regarding laboratory parameters at admission or routine follow-up, lymphopenia (<1,5/1000 mm^3) was observed in 90% (10/11) of cases and thrombocytopenia (<150/1000 mm^3) in almost 50% (5/11) of cases. Troponin was higher in two out of three patients who died. Increased inflammatory markers were common and higher in those requiring intensive care (Table 2).

Chest tomography was performed in 82% (9/11) of patients, six presented less than 50% of bilateral pulmonary infiltrates with ground-glass opacity (GGO), and three had more than 50% of bilateral pulmonary infiltrates with ground-glass opacity associated with worse prognosis (Table 3).

Only one patient received hydroxychloroquine as an alternative therapy for COVID-19. None of the patients received remdesivir, because it was not approved for clinical use in our country until the

TABLE 1 Characteristics and COVID-19 symptoms in heart transplant patients

Inpatients/ outpatients*	Age (years)	Gender	Time from transplant (months)	Comorbidities	Immunosuppression	Symptoms
1	79	Male	264	HTN, DM, CRD	CyA, MMF, CSs	Fever, cough, dyspnea
2	67	Male	264	HTN, DM, CRD	mTOR, MMF, CSs	Cough, dyspnea
3	52	Female	192	HTN, DM, obesity	CyA, MMF, CSs	Fever, cough, dyspnea
4	50	Male	84	HTN, DM	CyA, mTOR, MMF, CSs	Fever, cough, GID
5	35	Female	3	DM	CyA, MMF, CSs	Fever, cough
6	69	Male	42	HTN, DM, CRD, obesity	CyA, mTOR, CSs	Fever, cough, dyspnea, GID
7	51	Male	72	HTN, DM, CRD	CyA, mTOR, MMF, CSs	Fever, cough, dyspnea
8	74	Male	124	HTN, DM, CRD	CyA, mTOR, CSs	GID
9*	37	Male	11	HTN	CyA, MMF, CSs	Fever
10*	73	Male	223	HTN, DM, CRD	CyA, MMF, CSs	No symptoms
11	44	Male	36	HTN	CyA, MMF, CSs	Fever, cough, GID

Note: Abbreviations: CRD, chronic renal disease; CSs, corticosteroids; CyA, cyclosporine A; DM, diabetes mellitus; GID, gastrointestinal disorder; HTN, hypertension; MMF, mycophenolate mofetil; mTOR, mTOR inhibitor.

*Indicate which is outpatients and death individual.

time of this study. Hospital stay was 4–21 days, with death occurring in 3 patients (27.3%). Vasopressors and mechanical ventilation were used in 20% of patients. None patient received extracorporeal membrane oxygenation (Table 3).

4 | DISCUSSION

In this study, we described eleven COVID-19 cases from a heart transplant patient cohort routinely followed up in our hospital, including nine cases of severe or critical COVID-19, and 2 cases of mild-to-moderate ambulatory COVID-19. The nine severe or critical COVID-19 patients sought emergency care due to difficulty breathing, and all of them were hospitalized. The two mild-to-moderate cases were minimally asymptomatic, suspected of SARS-CoV-2 infection during a routine visit, confirmed by serology around two months after COVID-19 symptoms, and therefore, they did not go through thoracic tomography as well.

Notably, at the beginning of pandemic outbreak, all nasopharyngeal swabs were tested at government-designated referral laboratory, and samples were missed by logistic services (2 cases with RT-PCR results lost and other 2 cases no longer in the acute phase of infection during routine follow-up).

We observed a 27% (3/11) mortality rate, slightly higher than in another study,[7] which observed 15% (2/13) mortality rate. However, our result was close to that found by Latif et al[8] (32%; 7/22) and Bottio et al[9] (29.7%; 14/47), the largest cases in this population to date, in which the authors observed a double fatality rate in heart transplant recipients than in general population. The most common symptoms observed in our study group were similar to the report described in Spain,[10] as well as in a multicenter study from Italy.[9]

Four patients (36%) in this study required intensive care, all with higher than 1000 ng/ml D-dimer, and three with above 50% of bilateral pulmonary infiltrates and worse clinical outcomes, progressing to death. Although our hospital offers venous-arterial extracorporeal membrane oxygenation (VA-ECMO), one elder patient opted for palliative treatment and the family refused this treatment. Two others patients did not fulfill the ELSO guidelines,[11] and both died of septic shock.

Some authors observed an elevated D-dimer in individuals with COVID-19,[12–14] suggesting possible disseminated intravascular coagulation. Furthermore, the group that received low molecular weight heparin had a lower mortality rate.[15,16] Interestingly, like Singhvi et al,[17] no episodes of thromboembolic event were observed in our study. Half of our patients had higher than 1000 ng/ml D-dimer and none of them treated with anticoagulant therapy, because it was not recommended by the institutional guideline at that time. It is worth to mention that D-dimer is not routinely assessed in our service, and then, most of our patients have no baseline values assessed.

In this study, patients who had elevated circulating troponin, often present hemodynamic instability, vasoactive drugs were required and had worst outcomes, as the literature points out.[18] Furthermore, patients suffering from viral sepsis usually present myocardial injury and elevate circulating troponin. The cardiac troponin concentration is associated with early mortality, as well as postdischarge cardiovascular morbidity.[19]

The number of patients with lymphopenia (<1,5/1000 mm^3) and thrombocytopenia (<150/1000 mm^3) was higher in this study, 90% (10/11) and 45% (5/11), respectively, versus previous reports in

TABLE 2 Laboratory parameters of heart transplant patients with COVID-19

	Total leukocytes (1000 mm³)			Lymphocytes (1000 mm³)			Platelets (1000 mm³)		
Inpatients/ Outpatients*	Baseline	Admission/ Outpatient*	Discharge/ Death*	Baseline	Admission/ Outpatient*	Discharge/ Death*	Baseline	Admission/ Outpatient	Discharge/ Death*
1	4.9	6.1	13.7*	1.1	0.7	0*	253	117	153 *
2	6.8	9.8	14.7*	0.7	0.5	1.0*	139	146	41*
3	6.6	3.7	3.4	1.9	0.9	2.0	352	220	371
4	6.4	7.7	3.4	1.0	1.3	1.5	164	136	153
5	6.1	8.3	5.2	1.3	0.4	0.5	127	259	193
6	6.1	2.8	0.3*	1.0	0	0*	166	55	30 *
7	5.7	10.5	7.7	1.0	0.3	1.2	153	175	178
8	5.2	5.1	5.7	1.4	0.9	1.2	171	96	111
9*	9.4	9.6*	9.7	1.6	1.7*	3.2	256	180	216
10*	4.6	6.1*	6.1	1.1	1.3*	1.0	148	203	169
11	8.3	5.4	8.0	2.4	1.2	1.4	292	202	252

	Troponin I (ng/L)			D-dimer (ng/ml)			C-reactive protein (mg/dL)			B-type natriuretic peptide (pg/ml)		
Inpatients/ Outpatients*	Baseline	Admission/ Outpatient	Discharge/ Death*	Baseline	Admission/ Outpatient	Discharge/ Death*	Baseline	Admission/ Outpatient	Discharge/ Death*	Baseline	Admission/ Outpatient	Discharge/ Death*
1	0.01	NA	NA*	NA	1836	NA*	0.5	21	25*	231	NA	NA*
2	NA	0.41	NA*	NA	1397	NA*	25	40	8.8*	4200	8410	NA*
3	0.02	0.02	NA	NA	287	235	NA	7.1	1	1010	1230	910
4	0.04	0.01	NA	NA	NA	NA	0.5	2	0.5	2823	NA	NA
5	0.08	0.03	0.07	NA	675	NA	0.5	1.1	0.7	3810	2800	6250
6	0.02	0.12	1.42*	NA	4061	NA*	22	33.4	33*	2370	270	7.350*
7	0.01	0.07	0.02	2642	6933	NA	22	33	0.5	61	1074	174
8	0.01	0.01	0.01	NA	1839	1300	4.5	8.1	2.6	219	430	490
9*	0.01	0.01	0.01	NA	147	NA	0.5	0.5	0.5	89	84	105
	0.01	0.01	0.01	NA	NA	NA	NA	NA	NA	394	694	777
11	0.01	0.01	0.01	205	341	397	2	1.3	NA	311	242	397

Note: Abbreviations: NA, not accomplished.

*Indicate death patients.

TABLE 3 Diagnosis and clinical treatment of heart transplant patients with COVID-19

Inpatients/ outpatients*	Diagnosis method	Chest TC	Death	Hospital stay (days)	Acute renal failure	Intensive care unit	Vasoactive drugs	Mechanical ventilation	Therapeutic drugs
1	RT-PCR	<50%	Yes	4	Yes	Yes	No	No	AZ
2	RT-PCR	>50%	Yes	4	Yes	Yes	Yes	Yes	HCQ, AZ, CSs
3	RT-PCR	<50%	No	11	No	No	No	No	NA
4	Serology	<50%	No	5	Yes	No	No	No	AZ
5	RT-PCR	<50%	No	21	Yes	No	No	No	NA
6	RT-PCR	>50%	Yes	44	Yes	Yes	Yes	Yes	CSs
7	RT-PCR	>50%	No	22	Yes	Yes	No	No	AZ, CSs
8	Serology	<50%	No	9	Yes	No	No	No	NA
9*	Serology	NA	No	0	No	No	No	No	NA
10*	Serology	NA	No	0	No	No	No	No	NA
11	RT-PCR	<50%	No	6	Yes	No	No	No	NA

Note: Abbreviations: AZ, azithromycin; CSs, corticosteroids; HCQ, hydroxychloroquine; NA, not accomplished; RT-PCR, polymerase chain reaction.
*Indicate that 9 and 10 were outpatients.

nontransplanted and transplanted populations.[20,21] This was likely due to the use of immunosuppressant or an additional symptom of COVID-19.

Although in vitro studies suggest that mycophenolate mofetil is inhibitor of coronaviruses,[22] the interferon alpha combined with cyclosporine therapy was effective in reducing MERS-CoV replication.[23] On the other hand, immunosuppressive therapy can increase susceptibility to the infection, decreasing an effective response to the treatment. The high mortality rate in this study does not suggest beneficial protection of immunosuppression; further randomized studies are necessary to assess each immunosuppressant individually.

The small cohort from a sole transplantation center is one major limitation of this study. However, it seems to be a common limitation in studies involving heart transplant patients infected by SARS-CoV-2. One must acknowledge that we did not routinely test all patients; therefore, we might have underestimated the prevalence of COVID-19 in patients with heart transplantation. Unfortunately, given the limited national resources, it was possible only to test symptomatic individuals.

It is not possible to draw conclusions as to specific therapies for COVID-19, or in managing immunosuppression, from a small observational, noninterventional study such as this. However, it does provide insight into the scope and magnitude of the burden of the disease. We hope that data the described herein could help to clarify the pathogeneses of COVID-19 into the heart transplant context.

5 | CONCLUSION

Heart transplant patients had comparable symptoms and outcomes as the general population; the immunosuppressive therapy background did not appear to protect them. Patients who presented higher levels of troponin and D-dimer with higher GGO pulmonary infiltrates had worse outcomes. Studies with larger cohorts may contribute to clarifying the immunosuppressive effect on COVID-19 outcomes.

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CONFLICT OF INTEREST

The authors have no conflicts of interest regarding the content of this manuscript.

DATA AVAILABILITY STATEMENT

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

ORCID

Rafaela Vale de Miranda Soriano https://orcid.org/0000-0002-9372-0589
Joao Manoel Rossi Neto https://orcid.org/0000-0002-5959-9359
Carolina Casadei dos Santos https://orcid.org/0000-0002-8966-1977
Hui Tzu Lin-Wang https://orcid.org/0000-0002-7027-7748

REFERENCES

1. Ge H, Wang X, Yuan X, et al. The epidemiology and clinical information about COVID-19. *Eur J Clin Microbiol Infect Dis*. 2020;39(6):1011-1019: published online ahead of print. https://doi.org/10.1007/s10096-020-03874-z
2. Coronavírus/Brasil. Ministério da Saúde do Bras. 2020. https://covid.saude.gov.br/
3. Manuel O, López-Medrano F, Kaiser L, et al. Influenza and other respiratory virus infections in solid organ transplant recipients. *Clin Microbiol Infect*. 2014;20(s7):102-108. https://doi.org/10.1111/1469-0691.12595
4. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*.

2020;395(10229):1033-1034. https://doi.org/10.1016/S0140-6736(20)30628-0
5. Li F, Cai JDN. First cases of COVID-19 in heart transplantation from China. *J Hear Lung Transplant*. 2020;39(5):496-497. https://doi.org/10.1016/j.healun.2020.03.006
6. CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel. Centers of disease control and prevention. Published 2020. https://fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations
7. Ketcham SW, Adie SK, Malliett A, et al. Coronavirus disease-2019 in heart transplant recipients in Southeastern Michigan: A case series. *J Card Fail*. 2020;26(6):457-461. https://doi.org/10.1016/j.cardfail.2020.05.008
8. Latif F, Farr MA, Clerkin KJ, et al. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. *JAMA Cardiol*. 2020:e202159. https://doi.org/10.1001/jamacardio.2020.2159
9. Bottio T, Bagozzi L, Fiocco A, et al. COVID-19 in heart transplant recipients: a multi-center analysis of the Northern Italian outbreak. *JACC Hear Fail*. 2020;9(1):52-61. https://doi.org/10.1016/j.jchf.2020.10.009
10. Fernández-Ruiz M, Andrés A, Loinaz C, et al. COVID-19 in solid organ transplant recipients: A single-center case series from Spain. *Am J Transpl*. 2020;20(7):1849-1858. https://doi.org/10.1111/ajt.15929
11. Makdisi G, Wang IW. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. *J Thorac Dis*. 2015;7(7):E166-E176. https://doi.org/10.3978/j.issn.2072-1439.2015.07.17
12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu YCB. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3
14. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2019;2020:e201017. https://doi.org/10.1001/jamacardio.2020.1017
15. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099. https://doi.org/10.1111/jth.14817
16. Porfidia A, Pola R. Venous thromboembolism in COVID-19 patients. *J Thromb Haemost*. 2020;18(6):1516-1517. https://doi.org/10.1111/jth.14842
17. Singhvi A, Barghash M, Lala A, et al. Challenges in heart transplantation during COVID-19: A single-center experience. *J Hear Lung Transpl*. 2020;39(9):894-903. https://doi.org/10.1016/j.healun.2020.06.015
18. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-810. https://doi.org/10.1001/jamacardio.2020.0950
19. Frencken JF, Donker DW, Spitoni C, et al. Myocardial injury in patients with sepsis and its association with long-term outcome. *Circ Cardiovasc Qual Outcomes*. 2018;11(2):e004040. https://doi.org/10.1161/CIRCOUTCOMES.117.004040
20. Huang D, Lian X, Song F, et al. Clinical features of severe patients infected with 2019 novel coronavirus: a systematic review and meta-analysis. *Ann Transl Med*. 2020;8(9):576. https://doi.org/10.21037/atm-20-2124
21. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. *N Engl J Med*. 2020;382(25):2475-2477. https://doi.org/10.1056/NEJMc2011117
22. Shen L, Niu J, Wang C, et al. High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. *J Virol*. 2019;93(12):e00023–19. https://doi.org/10.1128/JVI.00023-19
23. Li HS, Kuok DIT, Cheung MC, et al. Effect of interferon alpha and cyclosporine treatment separately and in combination on Middle East Respiratory Syndrome Coronavirus (MERS-CoV) replication in a human in-vitro and ex-vivo culture model. *Antivir Res*. 2018;155:89-96. https://doi.org/10.1016/j.antiviral.2018.05.007

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