ORIGINAL ARTICLE

Coronavirus disease 2019 (COVID-19) in the heart transplant population: a single-centre experience

Raphael Caraffa [a,†], Lorenzo Bagozzi [a,†], Alessandro Fiocco [a], Olimpia Bifulco [a], Matteo Nadali[a], Matteo Ponzoni[a], Massimiliano Carrozzini [a], Giuseppe Toscano[a], Angela Pompea Fraiese[a], Marco Metra [b], Carlo Maria Lombardi[b], Francesco Serafini[c], Angela Ribola[d], Vjola Jorgji[e], Tomaso Bottio [a,*] and Gino Gerosa [a]

[a] Cardiac Surgery Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy
[b] Cardiology Unit, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health University, Spedali Civili of Brescia, Brescia, Italy
[c] Internal Medicine Unit, Ospedale Dell'Angelo, Mestre Venice, Italy
[d] Department of Anesthesia, Ospedale di Cremona, Cremona, Italy
[e] Hacohen Lab, Massachusetts General Hospital, Boston, MA, USA

* Corresponding author. Cardiac Surgery Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Via Giustiniani 2, 35128 Padua, Italy. Tel: +39-049-8212410; fax: +39-049-8212409; e-mail: tbottio@gmail.com; tomaso.bottio@unipd.it (T. Bottio).
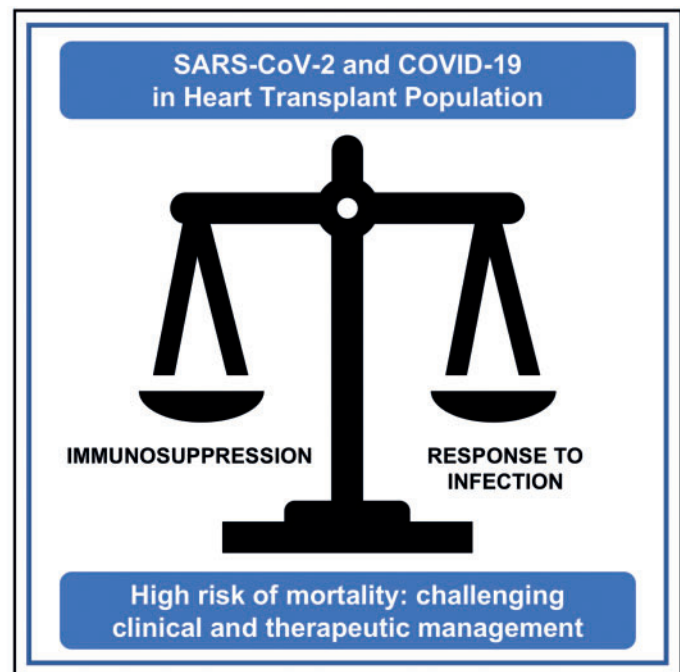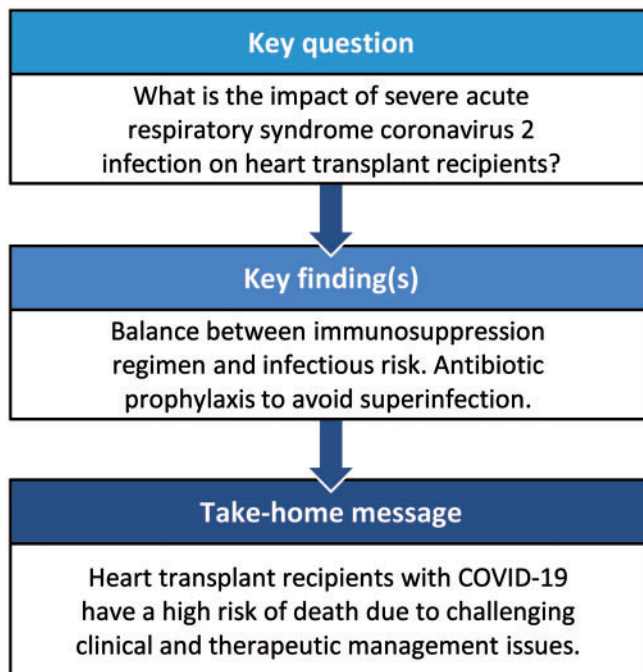
Abstract

OBJECTIVES: Few anecdotal cases have been reported in the literature regarding heart transplant recipients and infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We report our experience with 6 patients hospitalized in Northern Italy during the outbreak.

†These authors shared co-first authorship.

METHODS: Of the 396 living heart transplant recipients from 1985 to 2020 included in the study, 6 patients developed the novel 2019 coronavirus disease. Risk factors, last follow-up characteristics, onset presentation, in-hospital course of disease and blood examinations data were collected for these patients.

RESULTS: All patients were symptomatic and had positive results from a nasopharyngeal swab test for SARS-CoV-2. Of the 6 patients, 5 were hospitalized and 1 remained self-quarantined at home. Two patients died and 3 were discharged home. Two patients were admittted to the intensive care unit . Immunosuppressive therapy was modified with a median reduction comprising doses that were 50% cyclosporine and 50% mycophenolate. All patients received a medium-dose of corticosteroids as a bolus medication in addition to their therapy. All hospitalized patients received hydroxychloroquine; 2 patients received ritonavir/lopinavir. Broad-spectrum antibiotics for prophylaxis were administered to all. One patient had an ischaemic stroke and died of sepsis.

CONCLUSIONS: In the absence of any strong evidence regarding the treatment of heart transplant recipients infected with SARS-CoV-2, we faced a new challenge in managing viral infection in an immunosuppressed population. Because immunomodulation interaction with the infection seems to be crucial for developing severe forms of the disease, we managed to reduce immunosuppressive therapy by adding medium doses of corticosteroids. Despite the limited number of affected patients, this report suggests that special considerations should be given to treating coronavirus disease in the heart transplant recipient population.

Keywords: Heart transplant population and coronavirus disease • Severe acute respiratory syndrome coronavirus 2 • Immunosuppressive therapy • Heart transplant recipient

---

ABBREVIATIONS

COVID-19	Coronavirus disease 2019
IQR	Interquartile range
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

The worldwide spread of the novel coronavirus disease 2019 (COVID-19) pandemic, first identified in Wuhan, China, has created unprecedented challenges in the diagnosis and medical treatment of affected patients as well as in public health management. Northern Italy was the first Western region to deal with COVID-19 and the first whose organ transplant population had to face the pandemic [1]. Despite the significant mitigating measures adopted, as of 4 May 2020, a total of 96,478 cases (46% of the total number of Italian cases) and 15,822 deaths (58%) have been reported in Lombardy and Veneto, respectively [2].

Data on patients with heart transplants in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) era are still limited and mostly anecdotal [3–13]. Immunosuppression-related issues present the main concern in this special population. An abnormal inflammatory response has been hypothesized to play a crucial role in acquiring severe forms of COVID-19, mainly due to damage of one's own tissues and microcirculatory thrombophilia [14]. Importantly, it is well established that severe infections in the immunocompromised population dramatically influence both the care and prognosis of patients.

Asymptomatic carriers of the virus and patients with mild presentations of COVID-19 have been reported in the transplant recipient population, as have patients with more severe forms [3–13]. Despite the limited number of reported cases, significant heterogeneity dominates the clinical presentation patterns and challenges remain in fully characterizing risk factors. This uncertainty has opened up a great debate regarding immunomodulation interaction with the infection [15].

Immunomodulated recipients may present higher viral loads and shedding, resulting in greater infectivity and potential spread to other individuals and the transplant team. Moreover, drug–drug interactions with immunosuppressant medications need to be carefully evaluated and managed, particularly the interference of antiviral medications with calcineurin inhibitors and mammalian targets of rapamycin inhibitors metabolism [16].

Mortality data are only available from case reports and small case series. The scientific community still has no conclusive evidence as to whether or not outcomes in this population could be worse than those in immunocompetent patients.

Our goal was to report our single-centre experience related to the COVID-19-affected heart transplant population and our adopted strategies to mitigate the clinical presentation of the infection. Moreover, we investigated outcomes from balancing immunosuppression regimen and response to infection through our therapeutic management strategy.

METHODS

Study population

We considered patients who had orthotopic heart transplants in our centre from 1985 to 2020. Heart transplant recipients affected with COVID-19 were included in the present investigation. We collected data related to risk factors, last follow-up characteristics, COVID-19 onset presentation, in-hospital course of disease and results from blood tests.

Ethical statement

The use of data for scientific and research purposes is mentioned in the current informed consent in use at the Cardiac Surgery Unit of Padova. We guarantee to respect patient anonymity and professional secrecy, and we use the collected data and the statistical analyses of this study solely for the scientific uses granted in accordance with the law in force (General Data Protection Regulation).

Statistical analyses

Continuous variables are expressed as median and interquartile range (IQR); categorical variables are presented as count and

Table 1: Main characteristics of the 6 heart transplant patients with COVID-19

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Demographics						
Age (years)	69	82	65	71	62	50
Gender	Male	Male	Male	Male	Male	Female
Time from heart transplant (years)	5	16	11	1	22	13
Risk factors						
BMI (kg/m^2)	22.4	23.6	24.5	25.3	32.6	21.5
Arterial hypertension	-	+	+	+	+	+
Dyslipidaemia	-	+	+	-	+	-
Diabetes mellitus	-	-	-	-	-	-
Former smoker	+	-	-	-	-	-
Extracardiac arteriopathy	-	-	-	-	-	-
COPD	-	-	-	-	-	-
Stroke	-	-	-	-	-	-
Malignancy	-	-	+	-	-	+
GFR (ml/min)	80	40	71	82	48	85
Previous PCI	-	+	-	-	-	-
NYHA class	I	II	I	I	I	I
Immunosuppressive therapy (mg/day)						
Cyclosporine	120	120	160	200	135	70
Mycophenolate	1440	-	1440	1440	1440	-
Everolimus	-	-	-	-	-	2
COVID-19 onset						
Presenting symptoms						
Cough	+	+	+	+	+	+
Shortness of breath	+	+	+	+	+	+
Myalgia	-	+	+	+	+	+
Anosmia	-	-	+	+	+	+
Headache	-	-	-	-	+	+
Sinusitis	-	-	-	-	-	+
Gastrointestinal symptoms	-	-	-	-	+	+
NPS test	+	+	+	+	+	+
X-ray pneumonia signs	+	+		+	+	-
Fever peak (°C)	38.0	38.6	38.0	39.5	38.5	39.2
Hospitalization	+	+	+	+	+	-
SpO$_2$ at admission (%)	91	85	97	78	85	
Worst SpO$_2$ during hospitalization (%)	88	75	88	75	65	
Laboratory results at admission						
WBC count (cells per 10^9/l)	10.00	9.24	4.00	7.50	5.90	
Hb (g/dl)	10.0	13.5	12.0	13.7	13.5	
Platelets (cells per 10^9/l)	400	113	215	301	151	
Lymphocyte (cells per 109/l)	0.35	0.32	0.55	0.90	0.20	
CRP (mg/dl)	157	140	3.3	72	29	
PCT (ng/ml)	0.26		0.09	0	0	
Serum creatinine (mg/dl)	1.29	2.1	1.79	1.3	2	
Troponin I (ng/dl)	34		8	18	24	
LVEF (%)	55	45	70	55	50	
Treatment and outcomes						
Hydroxychloroquine	+	+	+	+	+	-
Lopinavir/ritonavir	+	-	-	-	+	-
Corticosteroid therapy	+	+	+	+	+	-
Modification of immunosuppressive therapy[a]	+	+	+	+	+	-
% Reduction of cyclosporine	40	100	60	50	40	0
% Reduction of mycophenolate	75	0	0	50	50	0
Antibiotics prophylaxis	+	+	+	+	+	+
ICU stay	+	-	-	-	+	
ICU length of stay	18	-	-	-	2	
High flow O$_2$	-	+	-	+	+	
NIV	-	+	-	+	+	
Intubation	+	-	-	-	-	
Complications						
Respiratory	-	ARDS	-	-	-	
Neurological	Ischaemic stroke	-	-	-	-	
Infective	Sepsis	-	-	-	-	
In-hospital length of stay	24	10	13	27	24	
Days to negative NPS test[b]			10	7	15	14[c]
Pronation	-	-	-	+	+	
Discharged	-	-	+	+	+	
Dead	+	+	-	-	-	-

[a]In-hospital percentage reduction from last follow-up dose of immunosuppressant.
[b]Days from first positive NPS test to first seriate negative NPS test and clinical resolution of symptoms.
[c]The patient has been asymptomatic since receiving the results of the first NPS test, which was repeated after 14 days, per government regulations.
ARDS: acute respiratory distress syndrome; BMI: body mass index; CRP: C-reactive protein; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; Hb: haemoglobin; ICU: intensive care unit; LVEF: left ventricular ejection fraction; NIV: non-invasive ventilation; NPS: naso-pharyngeal swab test; NYHA: New York heart association; PCI: percutaneous coronary intervention; PCT: procalcitonin; SpO$_2$: oxygen saturation; WBC: white blood cells.

frequency. All statistical analyses were performed using SPSS software version 20 (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA).

RESULTS

All collected data are shown in Table 1. To date, 396 heart transplant patients are still alive. Six patients developed active SARS-CoV-2 infection: 2 of these patients died, 1 of acute respiratory distress syndrome and the other of sepsis. All included patients who had heart transplants had the positive reverse transcriptase-polymerase chain reaction nasopharyngeal swab test for SARS-CoV-2 and were symptomatic with fever, cough and shortness of breath. Of the 6 patients, the only female in the study presented mild symptoms and remained in self-quarantine at home. The rest of our cohort was hospitalized in Northern Italy; they had moderate-to-severe symptoms, such as fever for more than 5 days, oxygen saturation below 90% requiring supportive care and signs of pneumonia on radiographs.

Risk factors

Data collected on risk factors are shown in Table 1. The median age was 67 years (IQR 59–74) and the median time from the heart transplant was 12 years (IQR 4–17.5). Among the patients' risk factors arterial hypertension was the most frequent, occurring in 83%, followed by dyslipidaemia in 50%. Only 1 patient was obese. The median glomerular filtration rate was 92 ml/min (IQR 79–133); no patients needed dialysis. At the last follow-up, all patients were classified as New York Heart Association functional class I with the exception of 1 in functional class II. One patient had a previous percutaneous coronary intervention procedure for a cardiac allograft vasculopathy. Graft function was preserved in all patients as evidenced by the last echocardiographic follow-up with a median left ventricular ejection fraction of 56% (IQR 53–58). Only 1 patient had a history of cellular-mediated rejection graded as moderate, 2R according to the International Society of Heart and Lung Transplantation classification of 2004, obtained in October 1997. Immunosuppressive therapy included cyclosporine for all patients, associated with mycophenolate in 4 cases and everolimus in 1 case.

In-hospital stay

Data are summarized in Table 1. Median in-hospital length of stay was 24 days (IQR 12–26). Three patients were discharged home and 2 patients died. Median oxygen saturation at admission was 85% (IQR 81–94), the worst level during hospitalization was 75% (IQR 70–88). All hospitalized patients had signs of pneumonia on radiographs. Troponin at admission fell consistently within the limits for all patients. Two patients needed time in the intensive care unit and invasive ventilation; both of them were then admitted to a ward; in 1 a tracheostomy was performed to wean the patient from ventilatory support. Pronation therapy was performed in 2 patients. One patient needed 3 days of continuous veno-venous hemofiltration therapy. One patient received inotropic drugs with noradrenaline at maximum doses of 0.1 mcg/kg/min for 3 days. Extracorporeal life support was never used. During the in-hospital stay echocardiographic monitoring was used to evaluate graft function. With the exception of a mild reduction in the left ventricular ejection fraction in an older patient with a heart transplant that was more than 20 years old, no patients showed any changes in cardiac function. One patient had an ischaemic stroke and a sputum culture that was positive for Pseudomonas; he required targeted antibiotics treatment; unfortunately he developed sepsis and then he died. The other patient developed acute respiratory distress syndrome and died of respiratory failure.

Pharmacological treatment

Collected data are provided in Table 1. During hospitalization hydroxychloroquine and broad-spectrum antibiotics for prophylaxis were administered to all patients. Ritonavir/lopinavir were used for 2 patients.

Our adopted strategy for immunosuppressive therapy comprised a median reduction of 50% (IQR 40–80) of cyclosporine doses and 50% (IQR 13–69) of mycophenolate. In all hospitalized patients, a 0.5–1 mg/kg/day bolus of prednisone was administered for the first 7 days. Those intubated or in serious condition were given an equivalent intravenous dose of methylprednisolone. Progressive tapering then followed, leading to a low maintenance dose of 5–10 mg/day at discharged. Immunosuppressive therapy remained reduced until the first outpatient follow-up examination. At that time, the original immunosuppressive regime was resumed and corticosteroid therapy was discontinued. No graft rejection episodes occurred.

The patient who self-quarantined at home was treated with a broad-spectrum antibiotic and had a rapid remission of symptoms and resolution of fever. No immunosuppressive therapy modifications were made and no anti-inflammatory agents were administered. The results of the nasopharyngeal swab test for SARS-CoV-2 at 14 days were negative.

DISCUSSION

Chronic immunosuppressive therapy in patients with heart transplants is framed in a well-established protocol that includes calcineurin inhibitors possibly in combination with purine synthesis inhibitors or mammalian targets of rapamycin inhibitors. This therapeutic scheme is effective in deactivating the lymphocytes of the adaptive immune response, which is primarily involved in viral infections.

Lacking any strong evidence regarding the treatment of patients with a heart transplant infected with SARS-CoV-2, we faced a new challenge in managing the viral infection in this immunosuppressed population. Strengthened by our experience with other viral infections in patients with heart transplants, especially cytomegalovirus, we followed the same management protocol in patients with COVID-19 [17]. Our first steps consisted of reducing immunosuppressive therapy in the patients with severe clinical forms of COVID-19, i.e. those with hypoxia who required hospitalization. This strategy was adopted due to the lymphocytopenia characterizing this syndrome. For the milder form of the disease (i.e. the patient in self-quarantine at home), we opted not to reduce immunosuppression, instead implementing a close telephone monitoring protocol.

Total suspension of immunosuppression has been proposed in some patients with kidney transplants and COVID-19 [18, 19]. However, we were concerned that suspending immunosuppression could lead to graft failure due to rebound activation of immunological memory, potentially exacerbated by the hyperinflammatory state.

Furthermore, we do not yet know if the anti-inflammatory effect of chronic immunosuppressive therapy plays an undetermined role in the 'cell damage cascade' triggered by an uncontrolled cytokine storm and lymphocyte–macrophage activation, as has already been speculated in the literature [20, 21]. Indeed, some evidence suggests that lung damage in the severe forms of the disease is essentially due to immune hyperactivation rather than viral pathogenesis *per se* [6].

Conversely, we know that pharmacological interferences occurs between the antiviral drugs used to treat SARS-CoV-2 and calcineurin inhibitors [16]. The main issue of drug–drug interactions is an increased in immunosuppressant plasma concentrations due to their shared metabolism via cytochrome-P_{450}-3A4. In particular, the interaction between lopinavir and calcineurin inhibitors has already been characterized as being based on suppression of cytochrome-P_{450}-3A4. In contrast, the interaction between hydroxychloroquine and calcineurin inhibitors is less clear. Its metabolism via cytochrome-P_{450}-3A4, as well as via cytochrome-P_{450}-2C8, might theoretically increase the plasma concentration of the immunosuppressant. Consequently, close monitoring of immunosuppressant levels is warranted.

Therefore, on one hand we chose to reduce chronic immunosuppressive therapy; on the other, we introduced corticosteroid therapy for 2 critical reasons.

First, we tried to reduce the hyperinflammatory state and the overproduction of inflammation mediators. However, the use of corticosteroids in SARS-CoV-2 infection for treatment of acute respiratory distress syndrome remains controversial [22]. A retrospective analysis by Wang *et al*. in a Wuhan cohort showed that administration of early, low-dose and short-term corticosteroids was associated with faster improvement of clinical symptoms and absorption of lung focus [23]. Moreover, Siddiqi and Mehra [20] proposed the use of corticosteroids in immunosuppressed states when hypoxia is highlighted in moderate to severe clinical scenarios. In this regard, supportive therapy with hydroxychloroquine was also administered in all hospitalized patients. At the beginning of the COVID-19 pandemic, first reports and many national treatment guidelines suggested the use of hydroxychloroquine due to the anti-inflammatory and broad-spectrum antiviral effects observed with the severe acute respiratory syndrome. However, despite its common use, efficacy and safety were not confirmed by several dedicated observational studies and randomized trials [24]. The U.S. Food and Drug Administration subsequently revoked emergency use authorization for the drug [25]. On 17 June 2020, the World Health Organization announced that the hydroxychloroquine arm of the Solidarity Trial was being stopped. Data from major ongoing randomized clinical trials showed that hydroxychloroquine does not result in a reduction in mortality of hospitalized COVID-19 patients, when compared with standard of care.

Only 2 of our 5 hospitalized patients were treated with ritonavir/lopinavir therapy. At the beginning of the Northern Italy pandemic, the Italian government agency for the regulation of drugs developed several protocols for off-label usage of antiretrovirals [26]. These 2 patients had fulfilled inclusion criteria for enrolment in one of the first randomized clinical trials for these drugs against COVID-19. With increasing evidence of both the absence of clinical benefit from ritonavir/lopinavir in the more seriously ill patients and the risk of toxicity associated with the combined administration of hydroxychloroquine and azithromycin, their usage in the general COVID-19 population has been limited. As a result, we have abandoned their use in our heart transplant population.

Second, by introducing corticosteroids, we lowered the risk of graft failure due to the reduction in the dose of immunosuppressants. Nevertheless, given the debated effects of corticosteroids, the dose introduced was of medium proportion, as already suggested [23]. Therefore, we hypothesize that the broad-spectrum immunomodulatory effect of corticosteroids can help in the clinical management of transplant recipients affected with severe forms of COVID-19.

Not least, we considered the administration of broad-spectrum antibiotic therapy to avoid superimposed bacterial infections that would have a detrimental effect on the prognosis due to immunosuppression and corticosteroids, and the reduction of defenses due to lymphocytopenia. We mainly opted for broad spectrum beta-lactams and macrolides.

The patient who self-quarantined at home, despite presenting with similar onset symptoms, experienced a mild course of infection of shorter duration. The nasopharyngeal swab test was performed when the person was already asymptomatic. This patient was the only one on everolimus due to a high number of Epstein-Barr virus copies. Although there are speculations about this drug's antiviral activity in relation to SARS-CoV-2, no conclusions can be drawn from a single case. Some authors claim a possible beneficial effect for everolimus as therapy for COVID-19 due to its immunomodulatory activity [27]. Moreover, the anti-replicative effect of controlling the spread of Epstein–Barr virus or cytomegalovirus can also be promising in SARS-CoV-2 infection on the basis of its ability to reduce mRNA translation, ribosome biogenesis, protein synthesis, mitochondrial metabolism and viral replication.

Table 2 summarizes the available data on SARS-COV-2 infections in heart transplant recipients from reported case series [3–13]. When we analysed the overall data, the case-fatality-rate was about 20%. More than 80% of the patients were hospitalized, and half required intensive care support. The best immunosuppressive strategy is still being debated, in accordance with 60% of dosage reduction cases.

The mortality rate remains higher compared to that of the overall population. It is still unclear whether any of the adopted approaches actually influence prognosis and survival.

Our adopted therapeutic strategy resulted in one-third mortality in this particular population at risk of severe illness from infection with the SARS-CoV-2. One patient of advanced age with an already documented cardiac allograft vasculopathy did not overcome the disease, having developed a severe form. Available data show a higher mortality rate among older male patients with cardiovascular comorbidities who are infected with SARS-CoV-2. Furthermore, we must consider that during the outbreak the maximum standard of care was not achievable for all due to the limited availability of intensive care unit beds. The other death was the consequence of a complicated course of hospitalization for a patient not responsive to antibiotic therapy who developed sepsis. In addition, in 1 case we even

Table 2: Summary of available data on SARS-COV-2 infections in heart transplant recipients

	Li *et al.* [3]	Mathies *et al.* [5]	Holzhauser *et al.* [6]	Hsu *et al.* [7]	Latif *et al.* [8]	Hoek *et al.* [9]	Kates *et al.* [10]	Decker *et al.* [11]	Fernandez-Ruiz *et al.* [12]	Lee *et al.* [13]	Caraffa *et al*	Total, *n* (%)
Number of patients	2	1	2	1	28	4	1	1	4	4	6	54
Baseline characteristics												
Age (years)	51; 43	77	59; 75	39	64 (53.3–70.5)	75; 65; 51; 50	74	62	64; 67; 63; 38	15; 25; 1.1; 2.4	67 (59–74)	59.1
Time from HTx (years)	16.2; 2.6	17	8; 20	3	8.6 (4.2–14.5)	21; 10; 10; 6	23	0.4	13.8; 10; 17.9; 8.7	0.4; 3; 0.5; 2	12 (4.0–17.5)	9.4
Male gender	2	1	1	1	22	3	1	1	4	1	5	42 (78)
Arterial hypertension	0	1	2	1	20	NA	NA	0	2	0	5	31 (63)
Diabetes mellitus	0	1	2	1	17	NA	NA	0	1	0	0	22 (45)
Chronic kidney disease[a]	0	1	2	0	10	NA	NA	0	0	0	0	13 (27)
Lung disease	0	0	0	1	10	NA	NA	1	1	0	0	13 (27)
PCI for CAV	0	1	0	0	NA	NA	NA	0	1	0	1	3 (14)
BMI >30	0	0	0	1	NA	NA	NA	0	NA	0	1	2 (12)
COVID-19 onset symptoms												
Fever	2	0	2	0	19	NA	1	1	4	3	6	38 (78)
Chest pain	0	0	0	1	5	NA	0	0	0	1	NA	7 (16)
Shortness of breath or cough	0	1	2	1	21	NA	1	1	4	2	6	39 (80)
Gastrointestinal symptoms	1	0	2	0	11	NA	0	0	1	1	2	18 (37)
Treatment regimens												
Maintenance immunosuppression												
Cyclosporine	0	0	1	0	5	1	0	1	3	2	6	19 (35)
Mycophenolate mofetil	2	1	2	1	19	2	0	1	4	1	4	37 (69)
Tacrolimus	2	0	1	1	22	3	1	0	1	1	0	32 (59)
Proliferation signal inhibitors	0	1	0	0	5	1	0	0	0	0	1	8 (15)
Azathioprine	0	0	0	0	0	0	0	0	0	2	0	2 (4)
Prednisone	0	0	0	1	19	2	0	1	4	2	0	29 (54)
Number of immunosuppressive medications												
1	0	0	0	0	3	0	1	0	0	0	1	2 (8)
2	2	1	2	0	8	3	0	0	0	1	5	14 (14)
3	0	0	0	1	16	1	0	1	4	2	0	9 (35)
4	0	0	0	0	1	0	0	0	0	0	0	0 (0)
COVID-19 treatment												
Hydroxychloroquine	0	1	2	1	18	3	0	1	4	1	5	36 (67)
Lopinavir/ritonavir	0	0	1	0	0	0	0	0	2	0	2	5 (9)
Remdesivir/placebo	0	0	0	1	0	0	0	0	0	0	0	1 (2)
Umifenovir	1	0	0	0	0	0	0	0	0	0	0	1 (2)
Oseltamivir	0	0	1	0	0	0	0	0	0	0	0	1 (2)
Ribavirin	1	0	0	0	0	0	0	0	0	0	0	1 (2)
IFN-b	0	0	0	0	0	0	0	0	1	0	0	1 (2)
Ganciclovir	2	1	0	0	0	0	0	0	0	0	0	3 (6)
Tocilizumab	0	0	2	0	6	0	0	0	0	0	0	8 (15)
Steroid bolus	1	0	1	0	8	0	0	1	0	1	5	17 (31)
IVIG	1	0	1	0	0	0	0	0	0	0	0	2 (4)
Immunosuppressant strategy												
Dose reduction	0	0	0	0	6	NA	0	0	0	1	5	12 (24)
At least 1 withdrawal	1	1	2	1	16	NA	0	0	4	1	1	27 (55)
Acute graft rejection	0	0	0	0	0	NA	0	0	0	0	0	0 (0)
Major outcomes												
Hospitalized	2	1	2	1	22	NA	0	1	4	2	5	40 (82)
Need for ICU stay	0	1	1	1	NA	NA	0	0	2	0	2	7 (33)
Invasive ventilation	0	0	1	0	NA	NA	0	0	2	0	1	4 (19)
Self quarantine at home	0	0	0	0	6	NA	1	0	0	2	1	10 (20)
Death	0	0	0	0	7	1	0	0	1	0	2	11 (20)
Discharged	2	1	1	1	11	NA	0	0	2	2	3	23 (47)
Remained hospitalized	0	0	1	0	4	NA	0	1	1	0	0	7 (14)

BMI: body mass index; CAV: cardiac allograft vasculopathy; HTx: heart transplant; IFN-b: interferon-beta; ICU: intensive care unit; IVIG: intravenous gamma globulin; NA: not available; PCI: percutaneous coronary intervention; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

[a]Defined by a glomerular filtration rate <30 ml/min and the presence of haemodialysis.

managed to treat the infection at home in an unprecedented era in which healthcare resources are limited by the pandemic.

Apart from a bacterial superinfection and progression of respiratory disease, the only major complication that occurred during hospitalization was an ischaemic stroke. Anecdotal cases regarding neurological events in patients with COVID-19 have been reported in the literature to date [28] and evidenced shows a hypercoagulability state in patients with severe forms [29]. Further investigations are needed to understand the aetiopathogenesis of this complication.

Limitations

The major limitations regarding our experience are related to the small size of the population studied. Months after the beginning of the pandemic, mounting evidence is emerging for therapy and supportive care practices for managing COVID-19 infections. More studies are needed to evaluate and correlate clinical and laboratory data to support our immunosuppressive modification strategy. The cohort of heart transplant recipients makes up a minimal part of the affected population and the need to collect patients in a multicentre study remains essential.

CONCLUSION

To date, few anecdotal results have been reported in the literature regarding infection with SARS-CoV-2 in heart transplant recipients. Our strategy primarily consisted of lowering the dose of their immunosuppressive therapy facing the viral infection and introducing corticosteroids to reduce the hyperinflammatory state and the risk of graft failure. Despite the limited number of affected patients, this report suggests that special considerations should be given to COVID-19 in the heart transplant population. Given the information available in the literature, the case fatality rate for this vulnerable cohort is doubled that of the overall population and the best therapeutic strategy remains unclear. Prompt referral to a transplant centre following onset of first symptoms is required in order to treat the disease immediately and avoid progression to severe forms.

Conflict of interest: none declared.

Author contributions

Raphael Caraffa: Writing—original draft. **Lorenzo Bagozzi:** Data curation. **Alessandro Fiocco:** Writing—original draft. **Olimpia Bifulco:** Formal analysis. **Matteo Nadali:** Methodology. **Matteo Ponzoni:** Data curation. **Massimiliano Carrozzini:** Supervision. **Giuseppe Toscano:** Validation. **Angela Pompea Fraiese:** Validation. **Marco Metra:** Writing—review & editing. **Carlo Maria Lombardi:** Writing—review & editing. **Francesco Serafini:** Data curation. **Angela Ribola:** Data curation. **Vjola Jorgji:** Writing—review & editing. **Tomaso Bottio:** Conceptualization; Writing—review & editing. **Gino Gerosa:** Conceptualization.

Reviewer information

REFERENCES

[1] WHO. Coronavirus Disease 2019 (COVID-19) Situation Report—83. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200504-covid-19-sitrep-105.pdf?sfvrsn=4cdda8af_2 (4 May 2020, date last accessed).

[2] Istituto Superiore di Sanità. Sorveglianza Integrata COVID-19 in Italia. https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_4maggio%20ITA.pdf (4 May 2020, date last accessed).

[3] Li F, Cai J, Dong N. First cases of COVID-19 in heart transplantation from China. J Heart Lung Transplant 2020;39:496–7.

[4] Ren Z-L, Hu R, Weng Z-W, Zhang M, Ruan YL, Wu ZY *et al.* Epidemiological and clinical characteristics of heart transplant recipients during the 2019 coronavirus outbreak in Wuhan, China: a descriptive survey report. J Heart Lung Transplant 2020.

[5] Mathies D, Rauschning D, Wagner U, Mueller F, Maibaum M, Binnemann C *et al.* A case of SARS-CoV-2 pneumonia with successful antiviral therapy in a 77-year-old man with a heart transplant. Am J Transplant 2020;20:1925–9.

[6] Holzhauser L, Lourenco L, Sarswat N, Kim G, Chung B, Nguyen AB. Early experience of COVID-19 in 2 heart transplant recipients: case reports and review of treatment options. Am J Transplant 2020; doi:10.1111/ajt.15982.

[7] Hsu JJ, Gaynor P, Kamath M, Fan A, Al-Saffar F, Cruz D *et al.* COVID-19 in a high-risk dual heart and kidney transplant recipient. Am J Transplant 2020;20:1911–15.

[8] Latif F, Farr MA, Clerkin KJ, Habal MV, Takeda K, Naka Y *et al.* Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. JAMA Cardiol 2020 13;e202159.

[9] Hoek RAS, Manintveld OC, Betjes MGH, Hellemons ME, Seghers L, van Kampen JAA *et al.* Covid-19 in solid organ transplant recipients: a single center experience. Transpl Int 2020; doi:10.1111/tri.13662.

[10] Kates OS, Fisher CE, Stankiewicz-Karita HC, Shepherd AK, Church EC, Kapnadak SG *et al.* Earliest cases of coronavirus disease 2019 (COVID-19) identified in solid organ transplant recipients in the United States. Am J Transplant 2020;20:1885–90.

[11] Decker A, Welzel M, Laubner K, Grundmann S, Kochs G, Panning M *et al.* Prolonged SARS-CoV-2 shedding and mild course of COVID-19 in a patient after recent heart transplantation. Am J Transplant 2020; doi:10.1111/ajt.16133.

[12] Fernández-Ruiz M, Andrés A, Loinaz C, Delgado JF, López-Medrano F, San Juan R *et al.* COVID-19 in solid organ transplant recipients: a single-center case series from Spain. Am J Transplant 2020;20:1849–58.

[13] Lee H, Mantell BS, Richmond ME, Law SP, Zuckerman WA, Addonizio L *et al.* Varying presentations of COVID-19 in young heart transplant recipients: a case series. Pediatr Transplant 2020;e13780.

[14] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.

[15] Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? Lancet 2020;395:1111.

[16] Liverpool Drug Interaction Group. COVID-19 Drug Interactions. http://www.covid19-druginteractions.org (18 June 2020, date last accessed).

[17] Potena L, Solidoro P, Patrucco F, Borgese L. Treatment and prevention of cytomegalovirus infection in heart and lung transplantation: an update. Expert Opin Pharmacother 2016;17:1611–22.

[18] Gandolfini I, Delsante M, Fiaccadori E, Zaza G, Manenti L, Degli Antoni A *et al.* COVID-19 in kidney transplant recipients. Am J Transplant 2020;20:1941–3.

[19] Zhu L, Xu X, Ma K, Guan H, Chen S, Chen Z *et al.* Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant 2020;20:1859–63.

[20] Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant 2020;39:405–7.

[21] Romanelli A, Mascolo S. Immunosuppression drug-related and clinical manifestation of coronavirus disease 2019: a therapeutical hypothesis. Am J Transplant 2020;20:1947–8.

[22] Poston JT, Patel BK, Davis. AM. Management of critically ill adults with COVID-19. JAMA 2020.

[23] Yin W, Weiwei J, Qi H, Cheng W, Bajou W, Pan Z *et al.* Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. MedRxiv 2020.

[24] Geleris Y, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G *et al.* Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020;382:2411–18.

[25] U.S. Food & Drug Administration. FDA Letter Revoking of Emergency Use Authorization for Emergency Use of Chloroquine Phosphate and Hydroxychloroquine Sulfate. https://www.fda.gov/media/138945/download (15 June 2020, date last accessed).

[26] AIFA—Agenzia Italiana del Farmaco. Lopinavir/ritonavir nella terapia dei pazienti adulti con COVID-19. https://www.aifa.gov.it/documents/20142/0/lopinavir_ritonavir_02.04.2020.pdf/64b8cf03-acf1-e9fa-80fa-c6d3ecba5f7d (15 June 2020, date last accessed).

[27] Terrazzano G, Rubino V, Palatucci AT, Giovazzino A, Carriero F, Ruggiero G. An open question: is it rational to inhibit the mTor-dependent pathway as COVID-19 therapy? Front. Pharmacol 2020;11:856.

[28] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W *et al.* Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38.

[29] Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E *et al.* COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost 2020;120:998–1000.