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COVID-19 FEATURED PAPER

A case series of novel coronavirus infection in heart transplantation from 2 centers in the pandemic area in the North of Italy



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KEYWORDS:

heart transplantation;
COVID-19;
epidemiology;
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BACKGROUND: Little is known about the coronavirus SARS-CoV-2 disease (COVID-19) in solid organ transplanted patients. We here report a series of heart transplanted patients with COVID-19 from two centers of Italy.

METHODS: All heart transplanted patients of Transplant Centers of Bergamo and Torino with a microbiologically confirmed SARS-CoV-2 infection were enrolled. Data collection included clinical presentation, laboratory and radiological findings, treatment and outcome. Follow-up was performed by visit or phone.

RESULTS: From February to March 2020 twenty-six heart transplanted patients (age 62 ± 12 years; 77% males; time from transplant 10 ± 10 years; 69% with comorbidities) had a microbiologically confirmed COVID-19. The most frequent symptom was fever, followed by cough. Seventeen patients had a pneumonia, 8 of them severe pneumonia. Seven patients died (27%) and 17 (65%) were hospitalized. Discontinuation of immunosuppression was associated with death (71 vs 21%, $p=0.02$). Conversely, all patients receiving steroids survived ($p<0.001$). Patients who received heart transplantation during COVID-19 outbreak survived and no acute graft rejection occurred. Patients who died were older than survivors, had a longer time from transplant and a worse clinical presentation at diagnosis.

The current regimen enabled the prolonged survival and function of orthotopic cardiac xenografts in altogether 6 of 8 baboons, of which 4 were now added. These results exceed the threshold set by the Advisory Board of the International Society for Heart and Lung Transplantation.

CONCLUSIONS: COVID-19 has a significant impact on long term heart transplanted patients. Conversely, SARS-CoV-2 infection seems to have a limited influence on more recent transplants. Our

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experience may suggest that heart transplantation programs can be maintained even during the pandemic phase if specific and tailored paths to prevent and to limit virus transmission are provided.

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The new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in December 2019 and spread around the globe. Its disease (coronavirus disease 2019 [COVID-19]) was declared a pandemic on March 11, 2020. The most burdened countries are China, Italy, Republic of Korea, and the United States of America, and almost 6 million of cases have been diagnosed around the world.¹

Emerging reports suggest that case fatality rate ranges from 2% to 15% according to regions.^{2,3} In addition, SARS-CoV-2 infection has a higher incidence and case fatality rate among the elderly and those with chronic comorbidities.⁴

Immunosuppressed patients may have a different epidemiology. In fact, it is questioned whether immunosuppression may play a role in SARS-CoV-2 infection.⁵ It has been speculated that SARS-CoV-2 damages the host through 2 overlapping mechanisms; the first is the direct damage of the virus itself, and the second is an abnormal host response that may lead to a cytokine storm syndrome.⁶ In consideration of this pathogenetic hypothesis, anti-inflammatory therapy and immunosuppressive treatment have been proposed as potential rescue active treatments against the detrimental abnormal host response that may take place especially in the most severe forms of COVID-19. However, their efficacy in clinical practice has shown conflicting results.⁷

The characterization of patients with acquired immunosuppression with SARS-CoV-2 infection is needed. International societies of solid organ transplantation are working to provide guidance to help clinicians in the management of transplanted patients and facing the impact of COVID-19 on transplant programs. Particularly, it is still debated whether decreasing immunosuppressive therapy in COVID-19–infected solid organ transplant recipients is worthwhile and if maintaining transplantation programs is reasonable.⁸ Unfortunately, to date, data in the literature are lacking. Only few reports on solid organ–transplanted patients and 2 case series on heart-transplanted patients with COVID-19 have been published so far.^{9–13} Ren et al.¹⁴ reported a low rate of suspected cases of SARS-CoV-2 infection and no death in a series of 87 heart transplant patients; however, none had a laboratory confirmation of infection. Latif et al.¹² reported a case fatality rate of 25% in a series of 28 heart-transplanted patients with a confirmed diagnosis of COVID-19.

The aim of this study is to report a series of heart-transplanted patients with SARS-CoV-2 infection from 2 Heart Transplant Centers in the North of Italy describing clinical characteristics, prognosis, and the impact of COVID-19 on heart transplant programs.

Methods

All transplanted patients of the Heart Transplant Center of ASST Papa Giovanni XXIII Hospital of Bergamo and of the Heart and

Lung Transplant Center of Città della Salute e della Scienza University Hospital of Torino with a confirmed SARS-CoV-2 infection were enrolled. A confirmed case was any person with laboratory evidence of SARS-CoV-2 infection, irrespective of clinical signs and symptoms.¹⁵ Laboratory confirmation was performed by real-time reverse transcriptase–polymerase chain reaction on nasopharyngeal swabs.¹⁶

All patients were evaluated by a heart transplant specialist in conjunction with an infectious disease specialist. Data collection included anamnestic and demographic data, pharmacological treatment and immunosuppressive therapy, physical evaluation and clinical data at first medical contact, all laboratory and radiological findings performed after diagnosis, treatment, and follow-up. Follow-up was performed by direct or phone clinical examination.

Fever was defined as an axillary temperature of 37.5°C or higher. Leukopenia and lymphocytopenia were defined as a count of <4,000 and 1,500 cells per cubic millimeter, respectively. Severe pneumonia was defined at admission according to the American Thoracic Society guidelines for community-acquired pneumonia.¹⁷

Heart transplant programs in the COVID era

Since the outbreak of COVID-19 in Italy, specific protocols of infection restraint were applied and COVID-19–free paths were identified inside our hospitals. In particular, history of contacts with confirmed or suspected cases of COVID-19 was carefully investigated in both donors and recipients. Reverse transcriptase–polymerase chain reaction on bronchoalveolar lavage was performed in all donors, and only negative donors were considered. Before transplant, all recipients were tested with a nasopharyngeal swab and only negative patients were accepted for surgery. During surgery, before admission to a dedicated COVID-free intensive care unit, a second test on the bronchoalveolar lavage was performed to confirm the absence of virus. Induction and maintenance immunosuppressive therapy did not change. After intensive care unit (ICU) discharge, patients were followed in a COVID-19–free ward. Different paths for outpatients were also identified. The outpatient follow-up was regularly performed without changes in the scheduled program for the most recent transplanted patients. The follow-up of patients transplanted from more than 1 year was performed by phone and only urgent visits were carried out. Anyway, before entering the transplant center, all patients were routinely tested. If SARS-CoV-2 positive, they were followed in dedicated rooms, in dedicated catheterization and echo-Doppler laboratories.

Statistics

Continuous variables are presented as mean \pm SD or median and interquartile range and were compared with analysis of variance. Categorical variables are expressed as count and percentage. Differences between survivors and non-survivors were tested with *t*-test or with cross tabulations tables by the Fisher's exact test with Fisher's mid-*p*-value arrangement, as appropriate. A receiver operating characteristics analysis was performed to identify the most accurate variables to predict mortality. Cut-offs were

identified according to Youden's index. A two-sided p -value < 0.05 was considered statistically significant; all analyses were performed with SPSS 20.0 (IBM Corp, Armonk, NY).

Results

From the beginning of February to the end of March 2020, 26 heart-transplanted recipients had a microbiologically confirmed SARS-CoV-2 infection, among a total of 740 patients followed in 2 Heart Transplant Centers (incidence of SARS-CoV-2 infection of 3.5%, at least). The median follow-up was 21 days.^{11–25} During the follow-up, 7 deaths (27%) occurred and 17 patients were hospitalized (65%). Fifteen patients had a hospitalization or a scheduled in-hospital visit, whereas 4 patients had close contact with a confirmed case of COVID-19 in the 2 weeks before SARS-CoV-2 testing. Testing was performed in all symptomatic patients and in patients (regardless of symptoms) requiring outpatient clinic admission. We tested a total of 62 patients. Positive patients were older (62 ± 12 vs 46 ± 18 years, $p < 0.001$), more recently transplanted (heart transplantation [HTx] within 1 year in 35% vs 92%, $p < 0.001$), and with more comorbidities (69% vs 36%, $p < 0.01$) than the negative ones.

Baseline characteristics

Median age was 63 years (range, 22–77), and 20 (77%) patients were males. Mean time from transplant was 10 ±

10 years (median, 6). Mean ejection fraction was 60% ± 8%. Other clinical characteristics are shown in Table 1. Eighteen patients (69%) had at least 1 comorbidity. The most frequent ones were arterial hypertension and chronic kidney disease. Seven patients (27%) received HTx after the beginning of the COVID-19 outbreak in China. Immunosuppressive treatment is shown in Table 1. Cyclosporin was the most frequent calcineurin inhibitor (85%), and 8 patients (31%) received 3 immunosuppressive drugs including oral steroids.

Patients who died were older than those who survived (71 ± 6 vs 59 ± 12 years, respectively, $p < 0.01$) and had a higher incidence of chronic kidney disease and diabetes (57% vs 37%, $p = 0.02$ and 43% vs 5%, $p = 0.04$, respectively). All patients who received HTx after the beginning of the COVID-19 outbreak survived (100% vs 63% in other patients, $p = 0.04$), as did all patients receiving oral steroids (100% vs 42% in patients not on steroids, $p = 0.02$). No association between calcineurin inhibitors, trough levels, and adverse events was found.

Clinical presentation

Clinical presentation is described in Table 2. The most frequent symptom was fever (81%), followed by cough (62%); dyspnea and gastrointestinal symptoms were less frequent (31% and 23%, respectively). Cough or fever were present in all but 2 patients (88%). At presentation, the first

Table 1 Baseline Characteristics ($n = 26$)

Characteristic	Total ($n = 26$)	Non-survivors ($n = 7$)	Survivors ($n = 19$)	p -value
Age, years, median (IQR)	63 (58–72)	74 (66–76)	62 (53–64)	<0.01
Male sex, n (%)	20 (77)	5 (71)	15 (79)	0.4
Years from HTx, median (IQR)	6 (0.4–20)	13 (4–17)	5 (0.2–23)	0.4
Time from HTx <3 months, n (%)	7 (27)	0 (0)	7 (37)	0.04
Ejection fraction (%)	60 ± 8	59 ± 9	60 ± 8	0.6
Previous heart disease				
Ischemic cardiomyopathy, n (%)	15 (58)	4 (71)	11 (58)	0.9
Dilated cardiomyopathy, n (%)	7 (27)	2 (43)	5 (26)	
Other diseases, n (%)	4 (15)	1 (29)	3 (16)	
Pts without comorbidities, n (%)	8 (31)	1 (29)	7 (37)	0.2
Comorbidities				
Hypertension, n (%)	15 (58)	4 (43)	11 (58)	0.4
Chronic kidney disease stage ≥ 3 , n (%)	13 (50)	6 (57)	7 (37)	0.02
Hemodialysis, n (%)	5 (19)	2 (43)	3 (16)	0.2
Diabetes, n (%)	4 (15)	3 (43)	1 (5)	0.04
COPD, n (%)	1 (4)	0 (0)	1 (5)	0.4
Immunosuppressive treatment				
Cyclosporine, n (%)	22 (85)	7 (100)	15 (79)	0.1
Tacrolimus, n (%)	4 (15)	0 (0)	4 (21)	0.1
Everolimus, n (%)	11 (42)	4 (57)	7 (37)	0.2
Mycophenolate, n (%)	13 (50)	2 (29)	11 (58)	0.1
Azathioprine, n (%)	2 (8)	1 (14)	1 (5)	0.3
Steroids, n (%)	8 (31)	0 (0)	8 (42)	0.02
Number of immunosuppressors				
1 or 2 drugs, n (%)	18 (69)	7 (100)	11 (58)	0.02
3 drugs, n (%)	8 (31)	0 (0)	8 (42)	

Abbreviations: COPD, chronic obstructive pulmonary disease; HTx, heart transplantation; IQR, interquartile range.

Table 2 Clinical, Laboratory, and Radiological Findings

Finding	Total (n = 26)	Non-survivors (n = 7)	Survivors (n = 19)	p-value
Clinical presentation and physical evaluation				
Fever, n (%)	21 (81)	7 (100)	14 (74)	0.2
Cough, n (%)	16 (62)	6 (86)	10 (53)	0.1
Fever or cough, n (%)	23 (88)	7 (100)	16 (84)	0.9
Dyspnea, n (%)	8 (31)	4 (43)	4 (21)	0.2
Gastrointestinal symptoms, n (%)	6 (23)	0 (0)	6 (32)	0.06
Physical examination				
Respiratory rate, breaths per minute	14 (13–18)	30 (18–33)	14 (12–15)	<0.01
Oxygen saturation on room air, %	96 (90–98)	84 (84–92)	97 (96–98)	<0.01
Laboratory tests and radiological findings				
Leukocytes, cells/mm ³ , median (IQR)	4,500 (2,940–8,050)	4,160 (2,930–9,965)	4,500 (2,883–8,050)	1.0
Lymphocytes, cells/mm ³ , median (IQR)	800 (530–2,000)	695 (505–825)	800 (595–2,400)	0.4
C-reactive protein, mg/L, median (IQR)	27 (10–92)	91 (27–195)	20 (10–67)	0.03
Procalcitonin, ng/ml, median (IQR)	0.04 (0.01–0.24)	1.24 (0.57–1.57)	0.03(0.01–0.12)	<0.001
D-dimer, ng/ml, median (IQR)	2,425 (1,390–4,295)	1,685 (1,075–10,500)	2,425 (406–4,091)	0.8
Ferritin, μg/liter, median (IQR)	984 (195–1243)	991 (242–1747)	703 (177–1243)	0.5
Abnormal chest X-ray, n (%)	16 (62)	7 (100)	9 (47)	<0.01
Clinical diagnosis				
Pneumonia, n (%)	17 (66)	7 (100)	10 (53)	0.01
Severe pneumonia, n (%)	8 (31)	6 (86)	2 (11)	<0.001

Abbreviation: IQR, interquartile range.

symptom was fever (80%) or cough (52%). Gastrointestinal symptoms occurred only in patients taking mycophenolate.

At the first clinical evaluation, 11 patients (42%) had low oxygen saturation on room air, whereas 3 had oxygen desaturation at walk test. A respiratory rate higher than 14 breaths per minute was recorded in 10 patients (38%), and 5 patients (19%) had a partial pressure of oxygen lower than 65 mm Hg. Patients who died had a higher respiratory rate and lower oxygen saturation at the first clinical evaluation ($p < 0.01$ for both).

Radiological and laboratory findings

In all patients for whom a chest X-ray was performed, 16 patients (62%) presented signs of pneumonia. A computed tomography scan was performed in 6 patients, showing interstitial involvement with diffuse bilateral ground-glass opacities in all patients.

Laboratory tests are detailed in Table 2. Leukopenia was found in 13 patients (50%) and lymphopenia in 16 (62%). Elevated C-reactive protein was found in 15 patients (58%). Procalcitonin was high in 5 patients, all of them with pneumonia. Among laboratory findings, only high procalcitonin and C-reactive protein were associated with an adverse outcome, whereas all the other tests were not.

Adverse events

Seven patients died, all from respiratory failure, and in 2 of them pulmonary embolism was also present. Deaths occurred after a median of 8 days from hospitalization (range, 4–16 days). Seventeen patients (66%) had a

diagnosis of pneumonia, 8 of them (47%) with a severe form; among them only 1 survived ($p < 0.001$). On the other side, all patients without pneumonia were alive at the last clinical follow-up ($p = 0.01$). Seventeen patients required hospitalization, whereas 9 were home quarantined and received a daily phone follow-up. All hospitalized patients required oxygen administration for at least 1 day. During hospitalization, 7 patients had a progression of respiratory failure and ultimately died, regardless of ventilatory support. To date, no quarantined patient has been hospitalized and no death has occurred among outpatients. Four patients are still in hospital in stable conditions. During follow-up, all patients had a weekly nasopharyngeal swab and to date virus was no longer found in only 1 patient.

No patient had signs or symptoms consistent with acute graft rejection after detection of SARS-CoV-2. Particularly, no one had a reduction of systolic function at echo-Doppler. Furthermore, 7 patients underwent scheduled endomyocardial biopsies that were all negative, both for acute rejection and for myocardial involvement of SARS-CoV-2.

Among variables at first clinical contact, the best predictors of mortality were age higher than 65 years, procalcitonin higher than 0.5 ng/ml, and oxygen saturation on room air lower than 95%, with an area under the curve of 0.78, 0.94, and 0.89, respectively (Table 4).

Pharmacological treatment

Management of immunosuppressive treatment for COVID-19 is detailed in Table 3. As a treatment strategy, reduction of immunosuppression with discontinuation of one drug

Table 3 Treatment and Outcome ($n = 26$)

Treatment	Total ($n = 26$)	Non-survivors ($n = 7$)	Survivors ($n = 19$)	p -value
Management of immunosuppression				
Discontinuation of one or more immunosuppressors, n (%)	9 (35)	5 (71)	4 (21)	0.02
Oral or intravenous steroids, n (%)	14 (54)	0 (0)	14 (74)	<0.001
Subgroup of patients with pneumonia ($n = 17$)	8/17 (47)	0/7 (0)	8/10 (80)	<0.001
Treatment of infection				
Enoxaparin, n (%)	15 (58)	7 (100)	8 (42)	<0.01
Hydroxychloroquine, n (%)	18 (69)	7 (100)	11 (58)	0.02
Antibiotic therapy, n (%)	22 (85)	7 (100)	15 (79)	0.1
Antiviral therapy, n (%)	6 (23)	6 (86)	0 (0)	<0.001
Intravenous steroids, n (%)	7 (27)	0 (0)	7 (37)	0.04
Oxygen administration, n (%)	16 (62)	7 (100)	9 (47)	<0.01
CPAP, n (%)	5 (19)	5 (71)	0 (0)	<0.001
Outcomes				
Hospitalization, n (%)	17 (65)	7 (100)	10 (53)	0.01
Hospitalization in ICU, n (%)	5 (19)	5 (71)	0 (0)	<0.001

Abbreviations: CPAP, continuous positive airway pressure; ICU, intensive care unit.

Table 4 Predictors of Mortality, Transplantation Strategy, and Treatment Strategy

Predictors of mortality in COVID HTx patients	AUC	Sens/spec
• Age >65 years	0.78	86/67%
• Procalcitonin >0.5 ng/ml	0.94	100/89%
• Oxygen saturation on room air <95%	0.89	100/69%
Strategies to maintain HTx programs during COVID		
• Screening of donors with bronchoalveolar lavage. Exclude positive donors.		
• Screening of recipients with nasopharyngeal swab. Exclude positive recipients.		
• Selection of recipients according to urgent needs. If not urgent, consider low-risk patients only.		
Treatment strategy in COVID HTx patients		
• Avoid unneeded discontinuation of immunosuppressive treatment.		
• Continue oral steroids /consider i.v. steroids.		
• Hydroxychloroquine in symptomatic patients.		

Abbreviations: AUC, area under the curve; COVID, coronavirus disease; HTx, heart transplantation; i.v., intravenous; sens, sensitivity; spec, specificity.

was performed in 9 patients, whereas all other patients continued the same immunosuppressive regimen as before SARS-CoV-2 infection. The discontinued drugs were everolimus or mycophenolate, whereas cyclosporin and tacrolimus were always maintained. Four patients needed a reduction of mycophenolate because of leukopenia, and 7 patients required a reduction of daily dose of cyclosporin, tacrolimus, or everolimus because of interactions with antiviral treatment. Thirteen patients received steroids during COVID-19, 7 of them intravenously (methylprednisolone 1 mg/kg/day), whereas 6 continued oral prednisone. All patients on steroids survived. The association of steroids with better outcome was also confirmed when considering intravenous steroids only (100% vs 63% of patients, $p = 0.04$) or excluding patients without pneumonia (100% vs 22% of patients, $p < 0.001$).

Specific treatment for COVID-19 is detailed in Table 3. The treatment was regularly revised according to the emerging evidence in the literature. All patients received symptomatic treatment. Eighteen patients (69%) received oral hydroxychloroquine (median dose, 200 mg twice a day). No side effects were observed with hydroxychloroquine,

although a mild increase of immunosuppressors was recorded. Hydroxychloroquine was usually stopped after resolution of symptoms. Most patients (85%) received also empirical antibiotic treatment (first choice, macrolide and/or beta-lactam), although a superimposed bacterial infection was documented in 2 patients only. Six patients with severe pneumonia were treated with lopinavir or ritonavir. However, after a few days the antiviral treatment was discontinued in both patients because of lack of clinical benefit¹⁸ and because of significant pharmacological interactions with immunosuppressive treatment (i.e., increase of calcineurin inhibitors although levels were higher than twice from baseline). No patient received remdesivir, tocilizumab, or convalescent serum. No one had a QT interval >480 ms (mean corrected QT 455 ± 15 ms).

Discussion

To date, this is one of the largest series of solid organ transplant recipients with SARS-CoV-2 infection. The main results are the following: (1) COVID-19 has a high mortality and hospitalization rate in heart-transplanted patients; (2)

mortality is associated with age, comorbidities, worse presentation at the onset of symptoms, and a longer time from transplant; (3) patients who received HTx during the SARS-CoV-2 outbreak had a mild disease and no transplant-related complications; and (4) mortality rate was higher in those patients with a lower immunosuppressive therapy, whereas the use of steroids seemed to be protective.

This is a cohort from 2 centers in the North of Italy. The 2 centers are located in the epicenter of the Italian epidemic. Testing has been performed only in patients with symptoms or requiring outpatient clinic admission. Therefore, the real incidence in our cohort is probably underestimated. However, our data show that the incidence of SARS-CoV-2 infection in transplanted patients was higher than in the overall Italian population.¹⁹ The higher incidence may be related to the characteristics of transplanted patients and to a higher risk of exposure because of frequent hospital admissions. In fact, transplanted patients with COVID-19 were older than the overall Italian COVID-19 population. The cohort was even older than COVID-19 population described in China by Guan et al.²⁰ and the one reported in a meta-analysis by Rodriguez-Morales et al.²¹ Additionally, among COVID-19 heart-transplanted patients, there were more males than in the general Italian COVID-19 positive population (77% vs 57%). These data, however, are in line with the higher prevalence of males in the heart-transplanted population according to the Registry of the International Society for Heart and Lung Transplantation.²²

Moreover, the mortality rate of this cohort was higher than expected. In fact, in Italy, in the general population over 60 years, the mortality rate for COVID-19, the overall hospitalization rate, and the ICU hospitalization rate are 12.6%, 20.4%, and 4.5%, respectively. Our cohort showed alarmingly high rates of mortality, hospitalization, and ICU admission (27%, 65%, and 19%, respectively). Both the case fatality rate and baseline characteristics were similar to those recently reported by Latif et al.¹² The high case fatality rate observed in heart-transplanted patients may be due to the characteristics of the cohort evaluated in the analysis. Most of our cohort is represented by long-term heart-transplanted survivors. These patients are chronically exposed to a long immunosuppressive therapy and at high risk to develop side effects. Although they show good heart function, this population must be considered very fragile because of the presence of different comorbidities (i.e., chronic kidney disease) related to a long exposure to immunosuppressive drugs. In a transplanted cohort, the association of advanced age with time-dependent comorbidities, such as calcineurin inhibitor nephrotoxicity and other common complications of immunosuppressive therapy, may be detrimental. Also, these conditions often require frequent in-hospital visits, increasing the risk of exposure to SARS-CoV-2. These characteristics may therefore explain the higher incidence of SARS-CoV-2 infection, the more severe clinical presentation, and the higher mortality rate in transplanted patients. The incidence of infection appeared to be unrelated with time from transplant. However, all the recently transplanted patients survived and seemed less

prone to develop severe COVID-19 than those transplanted from a longer period.

Clinical presentation was similar to non-transplanted patients. The incidence of fever and cough was in line with previous reports. At least 1 of the 2 was present in almost all patients. Dyspnea at onset was less frequent and was not associated with adverse outcome. Gastrointestinal symptoms were significantly more frequent than in the overall COVID-19 population (23% vs 4–6%). It is difficult to explain this finding; however, all these patients were receiving mycophenolate, which may have gastrointestinal side effects. Physical evaluation and radiological examination suggesting severe pneumonia at onset were the most accurate predictors of worse outcome. The diagnostic and prognostic utility of laboratory findings may be challenged because immunosuppressive drugs may reduce the inflammatory response in transplanted patients. However, both C-reactive protein and procalcitonin were higher in patients who died, whereas leukopenia and lymphopenia were not.

During the COVID-19 outbreak, the management of immunosuppression is challenging. In our experience, reduction of immunosuppression could not provide a significant benefit and, on the contrary, this strategy was associated with a worse outcome. It must be recognized that it is not possible to discriminate if deterioration was related to this strategy or if it was the result of an independent progression of the disease and immunosuppression reduction only a marker of more severely ill patients. In our series, patients on oral steroids (required for the age of transplant, recent transplants, or because of recurrent acute rejection) did not have severe pneumonia or die. Moreover, all patients that received HTx within 3 months had a higher grade of immunosuppression (i.e., 3 immunosuppressive drugs) and did not develop a severe disease. These results are of interest because they support the theory of a protective role of immunosuppression in the control of cytokine storm syndrome related to virus infection.²³ However, it must be recognized that these results should be interpreted with caution owing to potential bias and residual confounders in this observational study with a small sample size, and more robust evidence is required. It should be also considered that patients who received HTx in the last 3 months were younger, had fewer comorbidities, and followed a strict protocol of mitigation strategies such as quarantine or social distancing. These characteristics may adequately explain the better observed outcome. No differences were found between the incidence of COVID-19 and the type of immunosuppressive agent, nor was their concentration associated with severity of COVID-19.

Once some evidence on the beneficial effect of methylprednisolone had emerged in the literature,²⁴ some of our patients received steroids as infection treatment. In our population, the use of intravenous steroids as infection therapy was not associated with severe COVID-19 or with progression of the viral disease, suggesting a limited impact on viral load. Although generalization is not possible, this may suggest that the treatment of acute rejection with intravenous steroid may not be contraindicated, and in the

evaluation between the risk of graft failure because of the presence of significant rejection and the potential worsening of viral infection because of corticosteroid therapy, the strategy may be in favor of rejection treatment.

This paper was intended to report the experience of 2 Italian centers on heart-transplanted recipients with SARS-CoV-2 infection and not to evaluate the efficacy of the suggested treatment for COVID-19.²⁵ This will be hopefully provided by ongoing randomized clinical trials (i.e., NCT04252664, NCT04257656, and ChiCTR2000029765). Patients requiring COVID-19-specific treatments (oxygen, enoxaparin, and hydroxychloroquine) had a worse outcome, but it must be considered that the sickest patients were those more likely to receive those treatments. However, it should be emphasized that patients tolerated hydroxychloroquine without significant pharmacological interactions with immunosuppression, whereas lopinavir and ritonavir were often discontinued because of significant drug interactions. Unfortunately, other rescue treatments (such as tocilizumab, remdesivir, or convalescent serum) were not used in our populations because some of them were not available and some of them were allowed exclusively in clinical trials.

Limitations

This analysis has some limitations. The observational nature of the study, the small sample size, and the lack of a comparison group do not allow us to draw definite conclusions on the association between outcome and clinical variables. In particular, the association between treatment (both triple immunosuppression and use of steroids) and outcome may depend on baseline differences among subgroups and not on the treatment itself. The high level of variation in therapy and baseline immunosuppression may confound the findings and limit interpretation of the association between treatment and outcome. Moreover, the individual impact of each single treatment cannot be adequately assessed as multiple therapies were given. Some cases had missing data. This limits the sample size further and the reliability of correlations. The follow-up is short and still ongoing; hence, late adverse events were not recorded. Finally, not all heart-transplanted patients in the 2 centers have been tested for SARS-CoV-2 and this cohort, deriving mostly from 2 COVID-19 hotbeds, could not be representative of the general population of heart-transplanted patients.

Conclusion

In conclusion, SARS-CoV-2 infection showed a high mortality in heart-transplanted patients, although it burdened mainly old and frail patients. In transplanted patients with COVID-19, discontinuation of immunosuppression is not supported by any evidence. On the contrary, in our cohort, it was associated with poor outcome, whereas the continuation or the initiation of steroids was associated with better outcome. Finally, although it is difficult to draw definitive indications based on our initial experience, recently transplanted patients with SARS-CoV-2 infection did not have a

poorer outcome. This pleads to maintain active the transplant programs even during the epidemic phase of the infection at least for life-saving organs. In our opinion, the critical points to keep the transplant activity as safe as possible are the following: (1) a favorable risk-to-benefit ratio between the urgent needs of the recipient and COVID-19-related risk; (2) the identification of COVID-19-free paths for the transplant centers, with periodical testing of both patients and personnel; (3) a meticulous screening of donor and recipient to demonstrate the absence of virus at the time of donation and transplant; and (4) an accurate donor-recipient matching reducing the post-operative risk, allowing a rapid discharge from ICU and hospital of the newly transplanted patients.

Disclosure statement

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