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LETTER TO THE EDITORS

An effective protocol for heart transplantation during COVID-19 outbreak

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The ongoing pandemic of novel coronavirus, SARS-CoV-2, and the severity of its disease (COVID-19) burdened solid organ transplantation (SOT) programmes [1]. In fact, healthcare facilities may be overcrowded to care COVID-19-infected patients, reducing organ donation with a significant impact on the number of transplant procedures. Moreover, the risk of viral transmission from SARS-CoV-2-positive donors and the risk of infection in transplanted patients are unknown. Very little is also known about the strategies to reduce the risk of COVID-19 in transplanted patients in terms of optimal immunosuppression regimen. International societies of SOT suggest extreme caution when considering transplantation in the COVID era and provide guidance based more on good sense than clear scientific evidence [2]. The simplest recommendation is to exclude all SARS-CoV-2-positive donors. However, virus detection cannot always be achieved both for logistical reasons both because tests for SARS-CoV-2 have a low sensitivity depending on the type of analysed biological samples (nasal versus nasopharyngeal swabs versus bronchoalveolar lavage, BAL) and on the stage of the disease (asymptomatic versus symptomatic). Radiologic assessment can also be considered to screen donors. However, chest X-ray is routinely used for donor assessment, but it has a very low sensitivity to detect viral infection. CT scan is surely more reliable although not feasible in every donation both for technical reasons and hemodynamic instability. Moreover, beside recommendations regarding transplantation in general, organ-specific guidelines are needed. In particular, for life-saving organs, it is critical to consider the interaction of three aspects: the urgency of transplant, the specific recipient characteristics and the transplant centre facilities. A tailored decision-making process that combines the previous mentioned factors is therefore recommended. In fact, the decision to proceed to transplant a patient or not should be based on several evaluations, such as the risk of death on the waiting list, the local prevalence of SARS-CoV-2, the diffusion of SARS-CoV-2 in the area of donation, the risk of severe COVID-19 after transplant, the availability of transplant centre resources to guarantee a rapid diagnosis of viral infection and a COVID-19-free path. A recent experience from Niguarda Hospital (Milan, Italy) provided the first data of feasibility of liver transplantation in selected patients [3]. We here describe our protocol for heart transplantation in the COVID era, and we report data on heart transplantation of the *Heart and Lung Transplant Centre of Città della Salute e della Scienza University Hospital* of Torino (Italy) during this period.

Our centre is located in Northern Italy, an area early and severely burdened by SARS-CoV-2. Since the outbreak of COVID-19, in Turin heart transplantation has continued and a dedicated protocol has been implemented in order to reduce the risk of donor-recipient, peri-operative and postoperative infection (see Fig. 1). According to the guidelines of the National Transplant Center (Centro Nazionale Trapianti, CNT), real-time reverse transcriptase-polymerase chain reaction on BAL is performed in all donors. Donors are tested at least once: always during the donation phase and in some cases before or immediately after admission to the intensive care unit. A careful evaluation based on anamnesis, laboratory results, chest X-ray and, if possible, CT scan is also carried out before donation. History of contacts with confirmed or suspected cases of COVID-19 is deeply investigated. A chest X-ray and laboratory tests (i.e. leucocyte and lymphocyte counts, C-reactive protein) are performed to rule out suspected COVID-19 findings.

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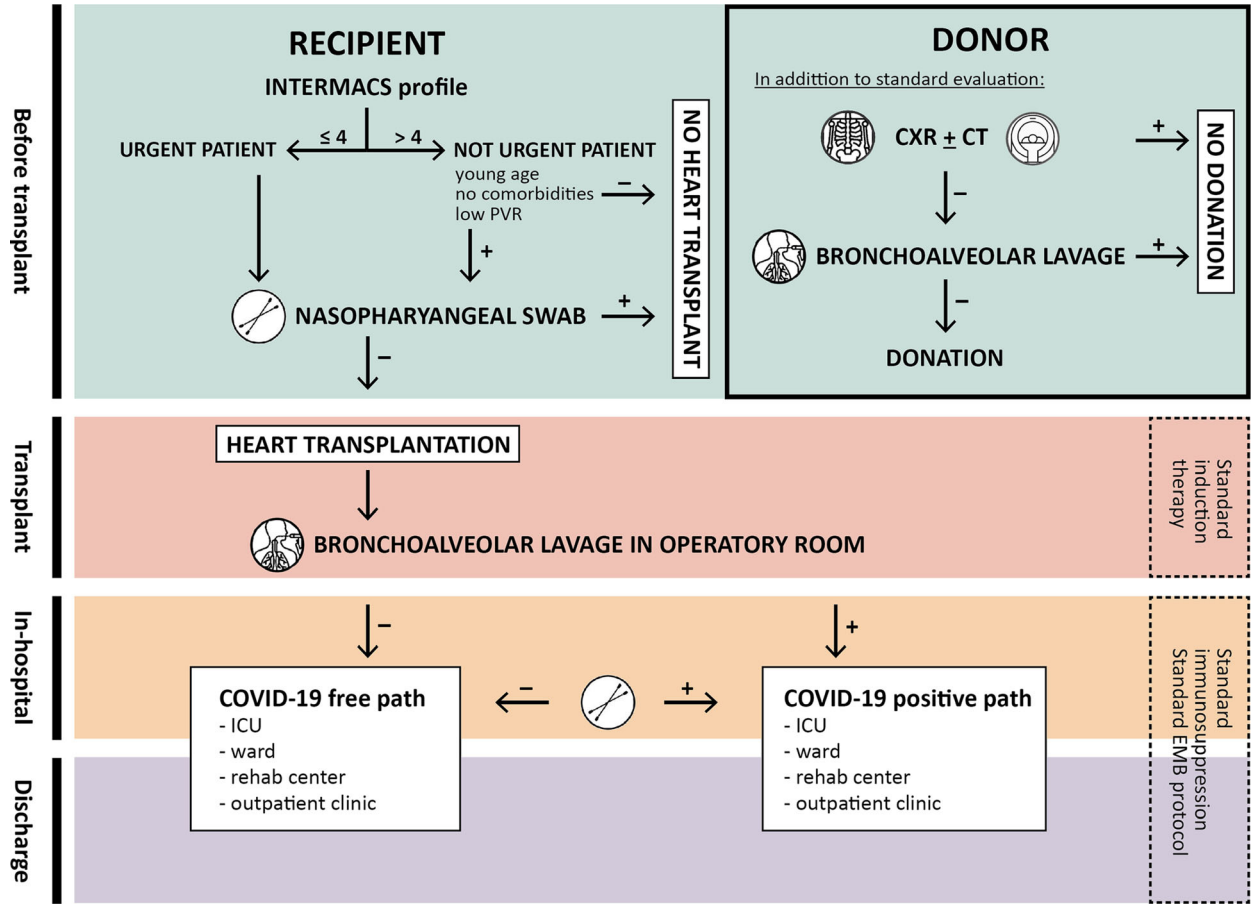

Figure 1 Screening and selection protocol for donor and recipient.

Anamnestic, radiological and laboratory findings are kept into consideration, independently from the result of bronchoalveolar lavage that must be necessarily negative. Only donors with a negative anamnesis, normal laboratory and radiological findings and negative BAL are ultimately considered suitable for donation.

Before transplant, all potential recipients are evaluated with anamnesis, laboratory results and chest X-ray. They are also tested with a nasopharyngeal swab immediately before transplant and only negative patients are accepted for surgery in dedicated COVID-19-free operatory rooms. Time constraint related with the procedure of heart transplant does not allow a double check with a second swab after 24 h before transplant. However, since there is evidence suggesting that BAL analysis is more sensitive than nasopharyngeal swab [4], during surgery, a second test on BAL is also performed to confirm the absence of the virus. During surgery, all involved personnel wear FFP3 masks in addition to usual PPE. The same is done for organ procurement. The number of people involved in the transplant procedure is limited as much as possible. Entry and exit from the operatory room are also reduced to the bare minimum. Moreover, if during surgery it is required to temporarily hold ventilation for surgical reasons, the ventilator is stopped without disconnection of the patient from the ventilator circuit to avoid potential spread of virus in the operating room. After surgery, two different paths (COVID-19-free, COVID-19-positive) have been identified inside the hospital to manage all the possible scenarios. Patients with a negative BAL are admitted to a dedicated COVID-19-free intensive care unit (ICU). A COVID-19 dedicated ICU is also available in the untoward event of a positive BAL, and the operating room is sanitized after surgery. Before ICU discharge, a nasopharyngeal swab is performed to transfer patients in a COVID-19-free or COVID-19-positive ward. Nasopharyngeal swabs are performed also before discharge from ward to rehabilitation centre and from rehabilitation centre to outpatient clinic in order to appropriately allocate the patient to a COVID-19-free or COVID-19-positive path.

Recipient selection is another critical issue. A careful evaluation of the risk-to-benefit ratio between the urgent needs of the recipient and its COVID-19-related risk is performed for the identification of the potential recipients. Patients requiring urgent heart transplant on the basis of hemodynamic status (i.e. INTERMACS profile ≤4) are always considered for transplantation, once provided they have not SARS-CoV-2 infection. On the other hand, for more stable recipients (INTERMACS profile >4) we consider those with a lower operative risk (young age, absence of comorbidities, less severe pulmonary hypertension), being in mind the dismal results of SARS-CoV-2 infection in patients with severe comorbidities in the general population [5]. Induction therapy is administered after the result of BAL. If BAL is negative, induction therapy is administered as usual. If positive, induction therapy is started only in patients at high risk for delayed calcineurin inhibitors administration (i.e. poor renal function). Maintenance immunosuppressive therapy has not changed. Usual endomyocardial biopsy protocol has been maintained (one biopsy every week for the first month, every two weeks up to the third month and monthly till the sixth month).

Since we adopted the described strategy, we have performed eleven heart transplants, and only one patient died on the waiting list. The mean age was 46 ± 18 years (median 55, range 17–59), 64% were males, 48% suffered from a dilated cardiomyopathy, and 3 had an INTERMACS profile ≤4. In comparison with the 14 patients transplanted from January to April 2019, patients transplanted in the COVID era (January-April 2020) were younger (median 55 vs. 62 years, $P = 0.06$) and had less comorbidities (36% vs. 71%, $P = 0.05$; no chronic kidney disease: 100% vs. 43%, $P < 0.01$). The patients transplanted in the COVID era had a lower degree of pulmonary hypertension (PVR >3 WU: 18% vs. 64%, $P = 0.01$). These data reflect the decision to transplant, among stable patients, only those with an expected uncomplicated postoperative period and shorter ICU stay. In-hospital and predischarge surveillance swabs were also all negative. Three patients resulted SARS-CoV-2 positive during follow-up. All of them were diagnosed 4, 6 and 7 weeks after discharge, respectively, and out of hospital transmission can be assumed. Two of them had mild symptoms (cough and fever), and the third remained completely asymptomatic. They were all home quarantined and received a daily phone follow-up. No change was made in the immunosuppression. After a minimum follow-up of three weeks from diagnosis, all of them are doing well. Since the COVID-19 outbreak, we have registered nine cases of SARS-CoV-2 infection in all our heart transplanted population. Asymptomatic patients have not received any specific treatment. Symptomatic patients have been put on oral hydroxychloroquine 200 mg bid and empirical antibiotic treatment (first choice macrolide and/or beta-lactam). Only patients with at least moderate symptoms have been hospitalized while patients with mild symptoms have been home quarantine with a phone follow-up.

In conclusion, our initial experience supports maintenance of transplant programmes for life-saving organs even during the epidemic phase of the infection. Our data confirm the efficacy of pretransplant screening for SARS-CoV-2 infection of both donors and recipients. Accurate selection of recipients according to clinical conditions and COVID-19-related risk may be critical, particularly during the worst phase of pandemic. Nevertheless, patients and their families are to be educated carefully to adopt mitigation measures to reduce SARS-CoV-2 infections after discharge. Though our experience is limited to heart transplant, our protocol may be of interest also for other solid organ transplant programmes.

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Conflicts of interest

There are no conflicts of interest.

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