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Practical Considerations for Solid Organ Transplantation During the COVID-19 Global Outbreak: The Experience from Singapore

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Abstract. The current coronavirus disease 2019 (COVID-19) pandemic has not only caused global social disruptions but has also put tremendous strain on healthcare systems worldwide. With all attention and significant effort diverted to containing and managing the COVID-19 outbreak (and understandably so), essential medical services such as transplant services are likely to be affected. Closure of transplant programs in an outbreak caused by a highly transmissible novel pathogen may be inevitable owing to patient safety. Yet program closure is not without harm; patients on the transplant waitlist may die before the program reopens. By adopting a tiered approach based on outbreak disease alert levels, and having hospital guidelines based on the best available evidence, life-saving transplants can still be safely performed. We performed a lung transplant and a liver transplant successfully during the COVID-19 era. We present our guidelines and experience on managing the transplant service as well as the selection and management of donors and recipients. We also discuss clinical dilemmas in the management COVID-19 in the posttransplant recipient.

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Because of the emergence of a novel coronavirus (now called Severe Acute Respiratory Distress Syndrome [SARS]-CoV-2, causing the disease coronavirus disease 2019 [COVID-19]) in Wuhan, China, in December 2019, there has been an exponential increase in the global number of confirmed cases. There are now >2 million cases in >200 countries. The ongoing COVID-19 outbreak has outstripped the 2003 SARS in scale and worldwide extent, leading the World Health Organization to officially declare it a pandemic on March 11, 2020.[1] The evolution of COVID-19 and the containment efforts to combat it are reminiscent of SARS. The potential for healthcare systems to be crippled by this pandemic is real and looming. Essential medical services may be affected, as hospitals commandeer resources to care for COVID-19 patients and suspects.[2] During SARS, cities experiencing community transmission, such as Singapore and Toronto, closed their transplant programs temporarily.[3,4] Although SARS came under control after a few months, allowing transplantation to resume, the current COVID-19 outbreak may be long-drawn. Organ transplantation is an essential medical service and cannot be put on hold indefinitely or for a prolonged period of time without compromising patients on the waiting list. Thus,

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while the medical community is largely focused on fighting this outbreak, we the transplant community have to evaluate how best to continue providing transplant care during these trying times.

Here, in Singapore, evidence of local transmission occurred shortly after the first imported cases were diagnosed.[5] Having survived the tragedy of SARS, our hospital had swung into crisis mode early, freeing the negative-pressure isolation ward of its usual patients (eg, those with tuberculosis, carbapenem-resistant *Enterobacteriaceae*) and reducing the number of elective surgeries to create bed capacity. Strict infection prevention protocols were implemented, and compliance audits were started. The heightened level of operations and the desire to maintain transplant as an essential service prompted us to develop internal guidelines on the selection and management of donors and recipients for transplantation in the setting of COVID-19. Shortly thereafter, a brain-dead donor was identified. We implemented these guidelines and proceeded to perform a deceased-donor lung and a liver transplant. The aim of this article is to share our experience in developing guidelines to continue provision of organ transplantation services during this pandemic. Specifically, we want to highlight the need for a tiered approach as the pandemic evolves.

EVOLVING EPIDEMIOLOGY OF COVID-19 AND ITS IMPACT ON DECISION FOR TRANSPLANT

The first reported cluster of SARS-CoV-2 infected individuals in December 2019 was reportedly linked to a large seafood and live animal market in Wuhan, Hubei Province, China, suggesting a zoonotic origin for this novel pathogen. Despite early closure of the market with attempts made to isolate suspects and closely monitor contacts, by mid-January 2020, COVID-19 had spread widely across China and exported cases were reported mainly in the Asia Pacific region, suggesting that human-to-human transmission (through droplets or direct contact) had become more common.[6-9] International travel further facilitated the global spread of COVID-19. As we now know, SARS-CoV-2 is highly transmissible with a reported reproduction number (R_0) between 1.4 and 5.5.[10] Asymptomatic and presymptomatic transmission before isolation, quarantine, social distancing, and community containment efforts likely contributed to the surge of cases globally.[6,8,11-13]

Based on current understanding of influenza pandemics,[14] we had anticipated that the COVID-19 outbreak would reach Singapore (and other parts of the world). Once human-to-human transmission was established, infections would be imported from affected areas resulting in the emergence of local clusters, and subsequently widespread community transmission with unlinked cases, particularly among densely populated cities like Singapore.[5,6,13]

As the situation was rapidly evolving, we envisioned a stratified decision-making process to allow our transplant service to respond to different phases of the pandemic. We developed a set of guidelines based on disease outbreak alert levels correlating with pandemic phases (Table 1). As the risk of transmission increases, a corresponding increase in caution must be exercised, restricting transplantation to those who require it urgently and cannot wait. Living donor transplantation activity, compared to deceased organ donation, will be reduced due to the need to protect the interests of the living donor.

In general, urgent transplants refer to patients with the following conditions: (1) liver failure with a high 28-d mortality; (2) heart failure patients who are on extracorporeal circulatory support, or mechanical circulatory support (MCS) with evidence of device-related complications or those who require continuous high-dose inotropic support; or (3) patients with end-stage lung disease who cannot sustain long on the waitlist. The urgency to perform liver transplantation for patients with hepatocellular carcinomas depends on their transplant oncologic profile and whether bridging therapy is an option. Two groups of patients who have a lower urgency for transplantation in a pandemic are (1) those with stable heart failure awaiting heart transplantation but are well-supported on MCS and (2) those with end-stage renal failure awaiting kidney transplantation but have no urgent issues with dialysis access.[15] Apart from urgency of transplant, an individualized risk assessment of the recipient based on the complexity of the transplant procedure, extent of medical comorbidities, and immunologic risk is also required. A medically and surgically complex candidate may require extraordinary resources such as an extended intensive care unit (ICU) stay, large amounts of blood products, or subspecialty support; these may not be promptly available when hospital resources and manpower are diverted away. The infective nature of SARS-CoV-2 and the implications on immunosuppression also imply that performing transplants with a higher immunological risk of rejection such as ABO-incompatible transplant or transplants for highly sensitized recipients may come at an increased risk. With that in mind, we developed a decision-making grid to guide patient selection for transplant (Figure 1). This balances the prioritization of a patient in the greatest need for that organ, against the principle of ideal patient selection for a procedure, by recognizing the fact that a successful patient outcome is intimately dependent on the resources that are available.

COVID-19 SITUATION IN SINGAPORE AND POLICY STATEMENTS FROM THE MINISTRY OF HEALTH

Singapore's first patient with COVID-19 was an imported case that was diagnosed at our hospital. Local transmission occurred within 2 wk and several local chains of transmission were later identified.[5] Through media reports, this sequence of events has been played out many times in different countries. In certain countries, even the earliest cases have not had travel links.[2,6] The ability to identify the local chains of transmission is attributed to the Singapore government establishing a Ministerial taskforce that, under the auspices of the Infectious Diseases Act, performed extensive contact tracing of infected and exposed individuals.

On February 19, 2020, the local Ministry of Health (MOH) issued a statement allowing living donor transplants to proceed, while temporarily banning all nonurgent deceased donor transplants.[15] As the epidemiologic curve of incident COVID-19 cases in Singapore flattened toward the end of February 2020, MOH allowed nonurgent deceased donor transplants as well, provided the earlier criteria were met (communication with MOH, Singapore on March 3, 2020). By then, our workgroup had developed guidelines on how we would proceed with transplantation safely. The thought processes and measures adopted are described in the subsequent sections.

TABLE 1.

Impact of disease outbreak alerts on transplantation programs

DORSCON alert[45] (transmission risk)	Extent of COVID-19 transmission	Deceased donor transplant program	Living donor transplant program
Green (low)	Transmission predominantly within Hubei Province, China Rare cases exported outside of China	Nil restrictions Organ donors with positive travel history to affected region may be rejected upon advice from TxID	Nil restrictions To defer transplant for 14–28 d if organ donors had positive contact history or travel history to affected areas
Yellow[a] (moderate)	Increased transmission to multiple provinces and municipalities in China Increasing number of exported cases outside of China Imported case to Singapore; no local transmission. No case fatality	Although restrictions not imposed, to proceed with transplant with caution Active screening[c] and exclusion of donors and recipients at risk of COVID-19 (based on history taking)	Nil restrictions. Thorough screening of donor and recipients through clinical history taking expected Active screening[c] of donors and recipients who are at risk of COVID-19 (based on history taking). To defer transplant for 14–28 d if screen positive
Orange[b] (elevated)	Widespread transmission within China Significant number of exported cases outside of China, in a few WHO regions. Reports of community transmission outside of China Local transmission WITHIN Singapore. Severe cases of COVID-19 reported	Some restrictions placed on transplant program. To proceed with extra caution.[d] Medically nonurgent transplants may be put on hold Precautions under DORSCON yellow apply. In addition, diagnostic testing to exclude COVID-19 is mandated for both donor and recipient	Restrictions may be imposed, to proceed with extra caution.[d] Living donor program transplant load expected to dip. Exceptions may be considered for urgent liver transplants Precautions under DORSCON yellow apply. In addition, diagnostic testing to exclude COVID-19 is for both donor and recipient
Red (very high)	Widespread global transmission Ongoing community transmission in Singapore Risk of increased number of severe infections Disruption of schools and businesses	Transplant surgeries are likely affected due to diversion of resources to combat COVID-19 Suspension of nonurgent transplant likely Medically urgent transplants to be considered on a case by case basis in consult with TxID. This is also dependent on available resources and restrictions imposed based on situation Precautions under DORSCON orange apply	Transplant surgeries are likely affected due to diversion of resources to combat COVID-19 Suspension of nonurgent transplant likely Medically urgent transplants to be considered on a case by case basis in consult with TxID. This is also dependent on available resources and restrictions imposed based on situation Precautions under DORSCON organ apply

[a]DORSCON alert was raised to yellow on January 21, 2020.
[b]DORSCON alert was raised to orange on February 7, 2020.
[c]Donors would have to be screened for respiratory symptoms and travel history to affected areas or CONTACT with COVID-19 cases or suspects through history taking.
[d]Decision to proceed with transplant is based on medical indication, and availability of manpower and resources. Medically urgent cases are given priority. Enhanced infection control precautions are put in place; restrictions are placed on the number of visitors, and healthcare workers attending to the transplant recipient.
COVID-19, coronavirus disease 19; DORSCON, Disease Outbreak Response System Condition; TxID, Transplant Infectious Diseases; WHO, World Health Organization.

MOH issued another advisory on April 6, 2020 permitting deceased donor organ transplants, and urgent living donor liver transplant, with the proviso that infection control measures pertaining to the transplant procedure were intact, and that there were available resources (eg, manpower, operating theater facilities, surgical and intensive care beds, blood stock, and adequacy of personal protective equipment [PPE]).[16] At the time of writing, Singapore is experiencing the second wave of COVID-19 infections, which occurred first from residents returning from other countries, followed by an emergence of new local clusters and cases of unlinked community transmission.

PRINCIPAL CONSIDERATIONS FOR NEW ORGAN TRANSPLANTATION DURING COVID-19

First and foremost, SARS-CoV-2 and the disease COVID-19 are still being defined. What we do not know is the (1) risk of transmission from a positive donor to a recipient, (2) impact of a recipient becoming infected with COVID-19 and how that influences transplant outcomes, and (3) effective treatment (if any) for COVID-19. With that in mind, the underlying principle (to allow safe transplants to continue) would be based on any available evidence and adopting best practices to exclude COVID-19 in the donor and the recipient, while maintaining a smooth operational workflow that also protects healthcare workers (HCWs).

MEASURES TO EXCLUDE COVID-19 IN DONORS AND RECIPIENTS

Our COVID-19–specific guidelines for donor and recipient assessment are described in Table 2. The differences in criteria for living donors and deceased donors stem from the time-sensitive nature of donation after brain death. The 14-d lead-up period for living donor transplantation is based on estimates that the median incubation period is approximately 5.1 d and that <1% will develop symptoms after 14 d of active monitoring or quarantine.[17] However, it would not be acceptable or practical to keep a brain-dead donor alive for that duration. The need for extensive testing has to be balanced against the need to expedite the evaluation process to free up ICU resources and allow a timely donation process that is acceptable to the donor family. Any COVID-19 suspect or case would automatically be excluded from donation. Donors with any potential risk of exposure to known COVID-19

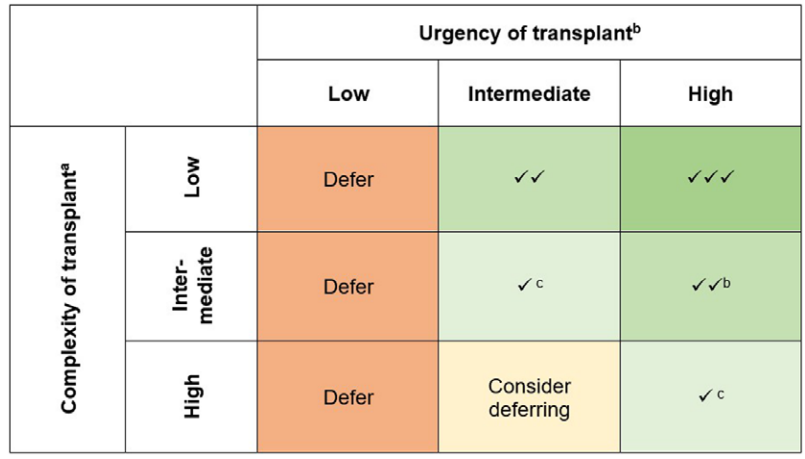

FIGURE 1. Decision-making grid on patient selection for transplant during pandemics. [a]The complexity of the transplant is determined by (a) surgical complexity, (b) extent of medical comorbidities, and (c) immunological risk. [b]In general, medically urgent transplants are performed for patients with (a) liver failure with a high 28-d mortality, (b) heart failure patients who are on MCS with evidence of device-related complications or those who require continuous high-dose inotropic support, or (c) patients with end-stage lung disease who cannot sustain long on the waitlist. Semiurgent transplants are indicated for patients with hepatocellular carcinomas. There is a low indication for transplant for stable heart failure patients who are well supported on MCS, and dialysis patients with no access issues. [c]Decision to proceed with transplantation is contingent on the availability of manpower, operating theater facilities, medical equipment, surgical and intensive care beds, blood products, and adequacy of PPE. MCS, mechanical circulatory support; PPE, personal protective equipment.

transmission routes (or fulfilling the case definition for a suspect case), such as recent travel history outside of Singapore, or possible relationship to any of locally identified COVID-19 clusters, are excluded. Donors would also undergo objective testing with SARS-CoV-2 polymerase chain reaction (PCR) from a respiratory specimen. Sequential testing also improves the sensitivity of the test, improving the confidence of ruling out COVID-19. For deceased donors, an additional computed tomography (CT) chest was performed even if SARS-CoV-2 PCR test is negative. This was based on published reports that CT imaging findings of viral pneumonia from COVID-19 predated PCR tests from respiratory samples, allowing for an earlier diagnosis.[18-20]

The criteria for potential transplant recipients are described in Table 2. In brief, they should not be suspected of, or infected with COVID-19. For patients requiring an urgent transplant, respiratory and febrile illnesses should be extensively evaluated to exclude COVID-19. For medically nonurgent transplants, a thorough history is taken from the recipients for the presence of respiratory symptoms or fever, as well as contact and travel history. Last, a COVID-19 test is performed as a final step to exclude asymptomatic COVID-19 infection before proceeding to surgery. For potential living donor transplant donors and recipients, we recommended an interim COVID-19 test at day 7 to proactively identify asymptomatic infection in the candidate that would allow the termination of the 14-d lead-up process to transplant.

TRANSPLANT CENTER POLICIES

Informed Consent for Transplant During COVID-19 Global Outbreak

An extra effort was made to counsel the recipients on the risks of proceeding with transplant given the evolving COVID-19 situation. We described existing steps and precautions adopted by the institution to exclude SARS-CoV-2 in both donor and recipient. We emphasized that COVID-19 may not be fully excluded despite these measures and that the natural history and management of COVID-19 infection in transplant recipients were not known. Ultimately, these have to be weighed against choosing to stay on the transplant waitlist and the risk of drop-out.

Infection Prevention Precautions

Hospital-wide infection prevention precautions were introduced in mid-January 2020. HCWs were also subject to mandatory twice-daily reporting of body temperature and a moratorium on future travel to affected countries. HCWs returning from affected areas were placed on a 14-d stay-home notice. HCWs who were unwell were directed to the staff clinic for prompt evaluation. All HCWs had to (at a minimum) wear a surgical mask in all clinical settings. HCWs in the isolation ward managing patients with or suspected of having COVID-19 wore full PPE, including N95 masks, face shield, long-sleeved gown, and gloves. Strict guidelines were laid down for surgeons and anesthetists in the operating room with regard to the use of appropriate PPE during procedures. Relevant to transplant, full PPE was used for aerosol-generating procedures such as intubation and extubation or surgery to the respiratory system. The N95 mask was worn if the Cavitron Ultrasonic Surgical Aspirator was used. The radiology unit screened all requests for investigations, creating a special workflow with segregated areas for patients with worrying clinical and epidemiological features.[21]

The SingHealth Duke-NUS Transplant program implemented its own business contingency plans. Those currently on or consulting for the inpatient transplant service were not allowed to attend to COVID-19 cases or suspects. A roster for an active and backup team(s) was drawn up where possible. For example, transplant coordinators were divided into 2 teams. This allowed the continuation of services if any team member became exposed to, or infected with COVID-19, necessitating the need to quarantine the HCWs and team members. As the donor team might need to travel to another hospital for organ procurement, donor and recipient teams were formed without overlap to further reduce the risk of

TABLE 2.

Donor and recipient selection criteria, and additional precautionary measures for transplant

	Living donor transplant program	Deceased donor transplant program
Donor selection criteria and instructions	In addition to fulfilling criteria for routine pretransplant workup, ALL of the following apply	Exclusion criteria
	- Absence of respiratory symptoms for at least 14 d before planned transplant	- Those with ANY travel history outside of Singapore in the last 28 d;
	- No travel history outside of Singapore for at least 14 d before planned transplant	- COVID-19 suspects/cases at the time of evaluation
	- Respiratory specimen (eg, nasopharyngeal or oropharyngeal specimen) test negative for SARS-Co-V2 PCR (×2)[a] before proceeding with transplant	In addition to fulfilling criteria for routine pretransplant workup, ALL of the following apply
	- Donors should not be COVID-19 suspects	(a) SARS-CoV-2 PCR (×3 specimens)[b] test negative
		AND
	- Normal CXR	(b) CT Chest with no evidence for viral pneumonia[c]
	The following precautions/advice are recommended:	Patients with negative SARS-CoV-2 PCR, and CT chest findings not suggestive of viral pneumonia may be considered as potential organ donors on a case by case basis in consult with TxID
	- Minimize hosting contacts with travel outside of locale (eg, overseas family/ friends)	
	- Avoid congregational/large group meetings (where possible) before planned transplant	
	- When participating in group activities, to wear a mask	
	- Practice social distancing	
	- Inform transplant coordinators if respiratory symptoms or febrile illness develops	
Recipient selection criteria and instructions	In addition to fulfilling criteria for routine pretransplant workup, ALL of the following apply	In addition to fulfilling criteria for routine pretransplant workup
	- Absence of respiratory symptoms for at least 14 d before planned transplant	For patients requiring a medically urgent transplant, ALL of the following apply
	- No travel history outside of Singapore for at least 14 d before planned transplant	- Should not be COVID-19 suspects
	- Respiratory specimen (eg, nasopharyngeal or oropharyngeal specimen) test negative for SARS-CoV-2 PCR (×2)[a] before proceeding with transplant	- Should be worked up for any respiratory symptoms/ fever, and COVID-19 ruled out before proceeding with transplant
	- Should not be COVID-19 suspects	- In the absences of respiratory symptoms, respiratory specimen (eg, nasopharyngeal or oropharyngeal specimen) must still test negative for SARS-CoV-2 PCR (×1) before transplant
	The following precautions/advice are recommended	For medically nonurgent transplant, ALL of the following apply
	- Minimize hosting contacts with travel outside of locale (eg, overseas family/ friends)	- Absence of respiratory symptoms for at least 14 d before planned transplant
	- Avoid congregational/large group meetings (where possible) before planned transplant	- No travel history outside of Singapore for at least 14 d before planned transplant
	- When participating in group activities, to wear a mask	- Respiratory specimen (eg, nasopharyngeal or oropharyngeal specimen) test negative for SARS-CoV-2 PCR (×1) just before proceeding with transplant
	- Practice social distancing	- Should not be COVID-19 suspects
	- Inform transplant coordinators if respiratory symptoms or febrile illness develops	
Posttransplant inpatient care for donor	Routine postsurgical care	NA
	Standard precautions[d]	
Posttransplant inpatient care for recipient	Recipient to be nursed strictly in a single room with droplet and standard precautions. Additional contact precautions for those who are colonized with multidrug resistant organisms	
	If febrile illness develops, to work up as appropriate[e]	
Instructions to appointed full time caregiver(s)	Have a dedicated full time caregiver	
	During the pretransplant period, the potential carer should, in the pretransplant period, adopt lifestyle restrictions that apply to the recipient. It is advisable that during the observation period for the recipient (as described above), the appointed full-time caregiver(s) remain free of respiratory symptoms. If they are unwell at any time before or after the transplant, they should inform the transplant coordinator, seek medical help/advice, practice social distancing and appoint an alternative caregiver for the potential recipient while they recuperate	

(*Continued*)

TABLE 2. (*Continued*)

Donor and recipient selection criteria, and additional precautionary measures for transplant

	Living donor transplant program	Deceased donor transplant program
	Advice to caregivers: - Minimize hosting contacts with travel outside of locale (eg, overseas family/friends) - Avoid congregational/large group meetings (where possible) before planned transplant - When participating in group activities, to wear a mask - Practice social distancing - Inform transplant coordinators if respiratory symptoms or febrile illness develops - Observe good personal hygiene - Be up to date with their yearly influenza vaccination	
Instructions to household member(s)	Advice to household members - Observe good personal hygiene - Be up to date with yearly influenza vaccination - For household members who are not the recipient's full-time caregivers: to wear a mask when they participate in group activities before and posttransplant	

[a]The first specimen should only be obtained after the first 7 d of the 14-d observation period for respiratory symptoms; the final specimen should be collected after a 14-d symptom-free period.
[b]Specimens collected for SARS-Co-V2 must be collected at least 12 h apart and the final SARS-CoV-2 PCR must be performed within 24–48 h of organ procurement.
[c]Patients with viral pneumonia other than COVID 19 (eg, rhinovirus, RSV, etc.) will be considered for suitability of organ donation on a case-by-case basis.
[d]Because of the outbreak of COVID-19, droplet precautions are instituted in all clinical care areas outside of isolation facilities.
[e]During the COVID-19 pandemic, COVID-19 has to be considered as a cause for unspecified febrile illness/respiratory tract infection. SARS-CoV-2 PCR and CT Chest to be considered as part of workup if appropriate.
COVID-19, coronavirus disease 19; CT, computed tomography; CXR, chest radiograph; PCR, polymerase chain reaction; SARS, Severe Acute Respiratory Distress Syndrome; TxID, transplant infectious diseases.

transmission among HCWs. When necessary, the back-table reconstruction was performed by the donor team in a separate operating room, before delivery of the organ to the recipient team. These measures taken by the hospital and transplant team were reviewed at various levels and deemed to allow safe provision of transplant care.

Postoperative Care

Recipients would be nursed strictly in a single room, with droplet and standard precautions. They would be monitored closely for the development of infective symptoms and tested for COVID-19 promptly, if indicated. In the unfortunate event that the recipient becomes positive for COVID-19, they will be managed in accordance to the hospital policy. All efforts will be made to establish if this was a donor-derived infection (DDI), hospital-acquired, or community-acquired. Hospital and MOH-sanctioned epidemiology teams would be engaged to perform the necessary contact tracing.

Additional Considerations

A key consideration before proceeding with transplant surgery is the availability of operating theater and ICU beds, as these resources may be diverted to the care of patients with COVID-19.[22] In addition, reduction of suitable blood donors and blood bank stores may compromise the success of transplant surgery in a coagulopathic patient. These factors may influence recipient selection and the decision to proceed with transplant.

CASE DESCRIPTION

In March 2020, when the Disease Outbreak Response System Condition (DORSCON) alert in Singapore was orange (see Table 1), a donation after brain-death donor was identified at another hospital. The cause of death was a cerebrovascular accident. Collateral history from the next-of-kin established that the potential donor did not have respiratory symptoms before admission. The donor fulfilled MOHs requirements for deceased donor evaluation, and fulfilled our criteria described in Table 2. We identified potential lung and liver recipients, who were called in to the hospital and evaluated. They too met our inclusion criteria and provided informed consent to proceed.

The recipient of both lungs was a middle-aged patient with postinfective bronchiectasis with pulmonary hypertension on long-term oxygen therapy but had no other comorbidities or prior chest surgery. Venous-arterial Extracorporeal Membrane Oxygenation was used for circulatory support and to maintain adequate gas exchange in a patient whose surgery was technically challenging; intraoperative blood transfusion requirements were also reduced with the use of a cell saver device. The liver recipient was a middle-aged patient with hepatocellular carcinoma and a low physiologic model for end-stage liver disease score. The patient was assessed to be a low surgical risk candidate and was expected to require minimal blood transfusions during surgery. Our usual immunosuppression protocol for lung and liver transplantation does not involve T-cell depleting induction therapy. Both patients received standard doses of steroid and basiliximab for induction. After transplant, they were maintained on tacrolimus (target trough level between 10–15 and 8–10 μg/L for the lung and the liver recipients, respectively), mycophenolate mofetil and followed a standard steroid taper.

Both recipients are negative for COVID-19 on postoperative day 15 and at the time of writing. The recipient of the lung transplant developed bilateral hemothorax, *Stenotrophomonas maltophilia* ventilator-associated pneumonia, and required prolonged ventilation due to diaphragmatic paralysis. The recipient of the liver has since been discharged to outpatient care.

DISCUSSION

Closure of a transplant program during an outbreak of a highly transmissible novel pathogen may be inevitable

because little is known about the pathogen. Invoking the tenet *Primum non nocere* in this setting means we have to consider the potential for transplant to cause harm by (1) introducing a DDI and (2) placing them at increased risk should they subsequently become infected with COVID-19 while immunosuppressed.

Detailed reviews of DDIs have not reported transmission of coronaviruses to guide evaluation or testing.[23,24] Because there is no known treatment for COVID-19, there is nothing that can be given empirically or prophylactically to prevent its transmission. Therefore, the only way to prevent COVID-19 DDI is by excluding infection in the donor. This may be achieved through history taking and confirmatory testing.[25]

A detailed history of the donor or from family members or witnesses (in the case of a deceased donor) may shed light on the donor's exposure to the pathogen. The policy of containment and extensive contact-tracing in Singapore has allowed the chains of transmission to be identified. In addition, MOH provides a daily press release with details on newly diagnosed patients with COVID-19 and sites of potential clusters.[5] This dynamic list of COVID-19 clusters is used at the Emergency Department when screening attendees and by organ procurement coordinators. Despite that, there exist several unlinked or yet-to-be linked cases. This implies that history taking alone is not foolproof in excluding COVID-19 and diagnostic tests are required to complete the evaluation.

The PCR assay for SARS-CoV-2 is now available at many centers. While a negative result may be used to rule out COVID-19, we do not know many of the parameters, such as the negative predictive value of this new test. Even among pathogens such as HIV, Hepatitis B and C that have established tests with a high negative predictive value, window period transmissions have been recorded.[26] Furthermore, a recent report of negative tests in a symptomatic patient that on repeat testing became positive is concerning, even though this may have been related to sampling or testing issues.[27]

We also considered testing for SARS-CoV-2 RNAemia in potential donors. RNAemia was documented in 15% of 41 patients in an early series from Wuhan.[28] RNAemia was seen in both patients that had milder symptoms, and those that required intensive care. Whether RNAemia translates to infection in solid organs such as the liver is unknown. Moreover, the period of RNAemia in relation to onset of the symptom was not described in the report by Huang et al.[28] The pervasiveness of SARS-CoV-2 in tissue and body fluids is also not fully defined. A unique feature of SARS-CoV-2 is its binding to angiotensin-converting enzyme 2 receptor and that it might demonstrate tropism to tissues with increased angiotensin-converting enzyme 2 expression, although this hypothesis has not been confirmed.[29] We know from the report by Chen et al[30] that among 9 pregnant women with COVID-19 who underwent delivery by cesarean section, there was no vertical transmission—SARS-CoV-2 was not identified in the amniotic fluid, cord blood, neonatal throat swab, and breast milk.

Presently, the MOH guideline stipulates that a donor must have 3 sequential negative throat swab PCR tests for SARS-CoV-2. These tests should ideally be taken at least 12 h apart, and within 24–48 h before organ donation. Our institution introduced the need for a CT chest as an added precaution after noting reports that CT chest findings predated a positive PCR result and could be used to identify patients with COVID-19.[18-20] In this case, we were sufficiently confident that the donor did not have COVID-19, given the clinical course in the ICU, the negative PCR tests and a negative CT chest.

The COVID-19 outbreak is evolving and we are currently in the acceleration phase of this pandemic. While halting transplantation may appear logical and in the interest of patient safety, it is also not without its harms. During SARS, deferring cancer treatment and postponing diagnostic testing led to what has been called the "collateral damage" of SARS.[4] The same applies to withholding life-saving transplants for patients on the waiting list who may risk dropping out because of progression of disease or death. This must be balanced against the challenges posed by COVID-19, which is likely to stay for some time. For this very reason, we have proposed a tiered approach to the selection of cases for transplantation.

Although we have addressed the issue of donor and recipient selection in the peritransplant period to prevent DDIs, we have to be cognizant that most COVID-19 infections in the posttransplant period are likely to be acquired from the community.[6,13] Nosocomial transmissions may still be possible but at our hospital, stringent infection prevention policies (described above) are in place to mitigate this risk. To safely navigate transplantation during this outbreak, we also have to recognize the importance of (1) prevention of COVID-19 in transplant recipients through old-school public health measures (eg, practice of good personal hygiene, appropriate use of face masks, isolation, quarantine, social distancing, and community containment of infected cases) in the absence of effective pharmacoprophylaxis[13,31] and (2) establishing and continually refining management and treatment strategies for infected transplant recipients based on available evidence.

Presently, there is little guidance on the management of the recipient should he or she get infected with COVID-19. Historical reports of other coronaviruses (SARS and Middle East Respiratory Syndrome) suggest that they may be lethal in transplant recipients. The liver transplant recipient described by Kumar et al[3] died from SARS. Of the 2 renal transplant patients of AlGhamdi et al[32] who acquired Middle East Respiratory Syndrome, 1 perished. Current published reports of posttransplant COVID-19 infections in transplant recipients were community acquired.[33-40] In addition, outcomes appear more severe. In a case series of 20 renal transplant recipients with COVID-19 by Alberici et al,[40] 85% of cases required supplementary oxygen therapy, 20% received ICU care, and the mortality rate was 25%, which is much higher than the case fatality rate of approximately 2.3% in the general population.[8] To improve outcomes of severe COVID-19 in recipients, it is intuitive then to consider either the use of antiviral therapy or modulation of immunosuppression as observed in these reports.[33-40] However, there are no proven benefits of either strategy and potential pitfalls exist.

With regard to antiviral therapy, there are no established therapies to date.[41] Although drugs such as hydroxychloroquine/chloroquine ± azithromycin, or lopinavir/ritonavir have in vivo activity against SARS-CoV-2, and are currently being used for patients with severe COVID-19, their efficacy is not proven and there may be adverse drug effects. Hydroxychloroquine/chloroquine ± azithromycin combination is associated with significant gastrointestinal disturbances and patients have to be closely monitoring for toxicity (in particular QTc prolongation). Lopinavir/ritonavir can also cause diarrhea. It is also a potent inhibitor of CYP 3A4, a dose adjustment of the calcineurin inhibitors (tacrolimus/

cyclosporine), is needed.[41,42] Preliminary data based on the compassionate use of remdesivir appear promising with 68% of patients showing clinical improvement.[43] This may be a possible therapeutic option, and we eagerly await the results of ongoing remdesivir clinical trials.[40] Where possible, we recommend the enrollment of affected patients into the remdesivir clinical trials. For those who do not qualify, we recommend the use of hydroxychloroquine. In patients with severe illness, the use of convalescent serum or immunomodulatory therapy with tocilizumab may be considered on a case-by-case basis.[44]

There is no strong evidence on how to modify immunosuppression during acute COVID-19. The severe illness associated with COVID-19 is associated with an intense inflammatory response. However, there is no proven benefit in the use of corticosteroids, and potential deleterious effects (eg, prolonged viral clearance and risk of secondary bacterial and fungal infections) exists.[41,44] On the other hand, it is also not entirely clear how to reduce or discontinue immunosuppression. Although it may bolster native immune responses, it risks graft rejection which will be a devastating complication due to the treatment required to reverse it. Presently, centers with experience managing COVID-19 in transplant recipients recommend dose reduction of antimetabolites or calcineurin inhibitors in those with severe infections.[41,42]

In this pandemic, the patient, transplanted or not, is similarly at the risk of succumbing to COVID-19 either as a patient with end-stage organ failure or immunosuppressed after transplant. At each phase of the outbreak, the decision to proceed with transplantation must be guided by the indication for transplant, availability of manpower and resources, and overall safety of all parties involved in the procedure. The known and unknown risks of transplantation are certainly increased amid this COVID-19 pandemic. However, these risks may be mitigated if the locale practices an effective containment policy, due to diligence made to exclude COVID-19 in both donor and recipient, and there are robust infectious prevention processes within the hospital. As more data emerge, it is likely that we will gain more knowledge to make the process even safer. Management strategies of COVID-19 after transplant will continue to evolve as more data emerge.

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