Letter to the editor

Utilization of SARS-COV-2 positive donors and recipients for liver transplantation in the pandemic era – An evidence-based review

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ABSTRACT

The current SARS-COV-2 pandemic led to a drastic drop in liver donation and transplantation in DDLT and LDLT settings. Living donations have decreased more than deceased organ donation due to the need to protect the interest of donors. In the SARS-COV-2 pandemic, major professional societies worldwide recommended against the use of organs from donors with acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. The basis for these recommendations are; SARS-CoV-2 could be transmitted to the recipient through organ transplantation and can result in severe manifestations; only limited effective targeted therapies are available, risk of transmission to the healthcare professionals, logistical limitations, and ethical concerns. In addition, end-stage liver disease patients on the waiting list represent vulnerable populations and are at higher risk for severe COVID-19 infection. Therefore, deferring life-saving transplants from COVID-positive donors during a pandemic may lead to more collateral damage by causing disease progression, increased death, and dropout from the waitlist. As this SARS-COV-2 pandemic is likely to stay with us for some time, we have to learn to co-exist with it. We believe that utilizing organs from mild/ asymptomatic COVID19 positive donors may expand the organ donor pool and mitigate disruptions in transplantation services during this pandemic.

Introduction

For various reasons, a drastic drop in liver donation and transplantation, both deceased donor (DDLT) and living donor liver transplantation (LDLT), occurred worldwide during the COVID-19 pandemic [1,2]. One of the critical reasons contributing to the decreased organ donation rates is excluding potential donors with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection from donations. Simultaneously, the safety of transplanting a recipient with SARS-COV-2 disease is unknown. Although there are emerging liver donation and transplantation reports from SARS-CoV-2-infected donors [3], optimal risk mitigation strategies are unclear. This review details the utilization of SARS-COV-2 positive donors in the pandemic era.

The restrictive national organ donation policy

At the start of SARS-COV-2 pandemic guidelines from the liver transplant Society of India (LTSI) [4] and other major professional societies worldwide have recommended against using organs from deceased donors with SARS-CoV-2 infection [5−7]. These recommendations were based on the prejudices that SARS-CoV-2 could be transmitted to the recipient through organ transplantation and can result in severe manifestations due to their immune-compromised status. Also, only limited effective targeted therapies are available if the recipient gets infected; there is a risk of transmission to healthcare professionals, logistical limitations, and ethical concerns [8,9]. However, today, standards of infection prevention are more defined, we can effectively and readily diagnose the infection, treatment options and vaccination do exist; all these were largely unavailable early in the pandemic. This enables us to take a 'shared decision' based upon the risk/benefit ratio associated with the transplantation of organs from SARS-CoV-2 infected donors. A recent guideline from Organ Procurement and Transplantation Network (OPTN)' states that transplantation decisions should balance the unknown virus transmission risk against the recipient's morbidity and mortality risk while awaiting transplantation.

Pioneering approach – thinking 'out of the box'

The SARS-COV-2 pandemic has led to a severe shortage of transplantable solid organs, both live and deceased ones. As a result, the transplant community will need to think beyond guidelines and recommendations to increase the number of life-saving transplants. Furthermore, with the persistent community transmission of SARS-CoV-2, transplant centers are increasingly likely to encounter many SARS-CoV-2 infected otherwise eligible donors, which we will discard if we stick to such a restrictive policy and the recipient will lose a valuable opportunity. With the changing face of a pandemic, it is high time that we reevaluate our current recommendations.

In December 2020, the National Transplant guidelines of Italy established that waitlisted patients who are SARS-CoV-2 positive or have a previous history of SARS-COV-2 can transplant with the heart and the liver from SARS-CoV-2 infected donors [10]. Insufficient data exist regarding the safety of transplanting organs recovered from donors with active SARS-COV-2 [8]. The first case was reported from South Korea in 2020, where a patient underwent ABO-incompatible LDLT from a COVID-19 infected liver donor inadvertently. The donor-derived transmission to the recipient was not identified [11]. A report from India subsequently demonstrated that elective liver transplantation early (two to four weeks) after COVID-19 infection is feasible in donors and recipients [12]. In an Italian multicenter series, no transmission was seen in ten recipients (eight had positive IgG against SARS-CoV-2 and two were asymptomatic COVID-19 positive at LT), who received liver organs from 9 active COVID-19 donors (liver biopsy negative for SARS-CoV-2 RNA in all at LT) [3]. In a recent case report, five uninfected recipients received seven non-lung abdominal organs (2 livers, one simultaneous liver and kidney, one kidney, and one simultaneous kidney and pancreas) from SARS-CoV-2−infected deceased donors. There was no evidence of virus transmission, and allograft biopsies showed no evidence of SARS-CoV-2 RNA. The author concluded that SARS-CoV-2 infected non-lung solid organs might be suitable for transplantation since hematogenous transmission has not been documented to date [13].

As per literature to date, there are 18 published instances of inadvertent donations from 11 SARS-CoV-2 infected donors without transmission (one living liver donor, one liver from deceased donors, one platelet transfusion, two allogeneic hematopoietic stem cell transplantations, and 13 kidneys) [11,14−17] and 24 instances, where non- lung organs (16 kidneys, 15 livers, and three hearts) were transplanted from SARS-CoV-2−infected donors without any virus transmission [11,16,18 −26]. There are several reports of non-lung organ transplantations (at least 45 kidneys, 14 livers, and six hearts from 55 donors) from donors with fully recovered COVID-19 infection with no evidence of virus transmission [11,18,27−36]. These data suggest that non-lung solid organs, including liver, from otherwise eligible donors with mild or asymptomatic active SARS-CoV-2 infections, can be a timely match for select urgent-need recipients. Such organs might safely increase the donor pool and serve as a life-saving opportunity for a needy recipient.

Considerations while utilizing organs from SARS-COV-2 infected donors

A general recommendation is that individuals with moderate to severe symptomatic SARS-CoV-2 infections should not proceed with living donor hepatectomy [6,7]. However, the safety of donors with a recent asymptomatic/mild infection is not known. The severity of COVID-19 disease was categorized as mild, moderate, severe, or critical, according to the clinical classification released by the WHO [37]. In addition, the third wave represents widespread community transmission of SARS-CoV-2′ delta' and 'omicron' variants associated with increased risk of transmission and asymptomatic infection, including in the vaccinated individuals [35]. Thus, we are very likely to encounter a scenario where an otherwise eligible donor without any symptoms will be detected positive for SARS-CoV-2 infection during screening for surgery. Deferring such otherwise medically suitable donors will result in the loss of significant numbers of organs for transplantation and an unnecessary delay in the LT.

Although, to date, there is no comprehensive data on the numbers of rejected organs due to COVID-19 positivity, based upon our personal experience, we assume donor organ rejection due to SARS-CoV-2 positivity is common, and its global impact on liver transplantation (LT) is underestimated. Most transplant teams made specific policy changes to their organ recovery protocols for safety during the pandemic. As a result, only 12−17% of the center's transplanted organs were from previously SARS-CoV-2-infected donors, mostly when the disease-to-donation interval was over a month [38].

Correlation between nasopharyngeal swab CT values, SARS-CoV-2 viremia, organotropism, and risk of transmission via non-lung organ transplantation

The most effective donor assessment method to estimate the risk of disease transmission from the donor to recipient in the community setting is unknown. Real-time polymerase chain reaction (RT-PCR) detects viral nucleic acid, and immunohistochemistry may demonstrate the presence of viral components in tissue. The 'cycling threshold' (CT) refers to the number of cycles required to exceed the established threshold to call a result positive [36]. Low cycling thresholds represent higher viral loads and vice versa. The presence of intact virions can be demonstrated by electron microscopy, while viral cultures are required to confirm the presence of intact virions capable of replication and infection.

Identifying SARS-CoV-2 RNA from a clinically asymptomatic patient with SARS-COV-2 infection may indicate two scenarios. It can be either a 'true asymptomatic early phase of infection' or 'a resolved infection' when there is no productive infection. The best kits currently available have sensitivity and specificity of 75% and 95%, respectively [39]. The 'cycle threshold,' an inverse correlate of the viral load, may help determine the likelihood of viremia. The viral load in SARS-CoV-2 peaks during the first week of illness and then gradually declines over the second week [40,41]. SARS-CoV-2 serology may also aid in assessing acute or resolved infection [42]. The angiotensin-converting Enzyme 2 receptors (ACE2), the portal of entry for SARS-CoV-2, and the priming cofactor, transmembrane serine protease 2 (TMPRSS2), are present throughout the body. Similarly, multiple organs and body fluids have shown the presence of SARS-CoV-2 RNA [43].

So based upon the above facts collectively, we are likely to think that a patient with a positive SARS-CoV-2 RT-PCR test with low Ct values will have more circulating virus in the blood, which will lead to pathologic organ infection and dysfunction. Hence we are also likely to think that hospitalized and critically ill donors of non-lung organs will have a potential higher risk of ongoing viremia and transmission than asymptomatic or minimally symptomatic donors.

Biological plausibility and circumstantial evidence alone cannot prove the infective virus. Only viral cultures can determine whether any transmissible virus was present in the extra-pulmonary organs. Further research is required to study and compare this risk of transmission between 'donor with recent symptomatic SARS-COV-2 infection with presumed low viral load' versus 'donor with recent symptomatic SARS-COV-2 infection with presumed high viral load' versus 'donor with prolonged hospitalization for severe SARS-COV-2 pneumonia'. Also, if the recipient gets infected from a donor organ, it would be essential to determine if the viral SARS-CoV-2 strain is the same in the donor compared to the recipient.

SARS-CoV-2 organotropism in non-lung tissues

Limited autopsy data to date do not demonstrate transmissible SARS-CoV-2 in non-lung solid organs that could be transplanted [44,45].

Severe SARS-COV-2 has been associated with hepatocellular injury; however, histologic manifestations of hepatitis specific to SARS-COV-2 are not fully understood. It can result from the direct cytopathic effect of the virus or systemic inflammatory response syndrome associated with it or maybe drug-induced [44].

Are other RNA respiratory viruses transmitted through organ transplantation?

Non-lung allografts from donors with other typical RNA respiratory viral infections, including influenza, are routinely accepted without the same concern for donor-derived infection despite being associated with viremia [46]. Like influenza, currently, the potential impact of SARS-CoV-2 in an exposed transplant recipient and health care workers can be mitigated through the availability of vaccination and treatment and can encourage us to accept organs from infected deceased donors.

Are we missing COVID+ donors and inadvertently transplanting their organs?

In a case report, SARS-CoV-2 was transmitted from lung donor to recipient despite negative donor upper respiratory tract testing [47]. The specificity of the best available kits is not 100%, and false-negative results are known attributable to several factors that can affect material adequacy and viral yields. It includes collection method, collection site, symptom duration, disease severity, viral mutations, and sampling expertise [39]. Hence, we believe there is a significant possibility of missing COVID+ donors and maybe transplanting their organs.

We recommend that lower respiratory testing for SARS-CoV-2 be performed routinely not only on all deceased lung donors but also in other solid organ donations. We acknowledge that the lower respiratory tract sampling is not consistent across centers, likely because of the unavailability of validated NAT assays for lower respiratory tract samples and logistical issues.

The risk of SARS-CoV-2 transmission through organ donation?

Publications to date have not reported SARS-CoV-2 donor-derived transmission in solid transplanted organs other than for lungs [48]. Even in cases with inadvertent usage of organs from SARS-CoV-2 infected donors, viral transmission events happened in none of the 12 recipients of extra-pulmonary organs, except for the three recipients of lungs [49,50]. Thus, as of now, there is no evidence that high nasopharyngeal swab Ct values correlate with viremia, organotropism, and a higher risk of transmission through non-lung organ donations. In summary, the risk for transplant-related transmission is low, especially among non-lung organ donors with mildly symptomatic or asymptomatic infection.

Donor safety in LDLT-outcomes of COVID-19 positive patients undergoing major surgery

The outcome of COVID-positive patients undergoing living donor hepatectomy is poorly defined. Case reports where COVID-19 infected donors were utilized for LT mainly were from deceased donors. Data on perioperative outcomes of COVID-19 infected patients undergoing non- LT major surgeries during first and second pandemic waves suggested an increased risk of intensive care unit (ICU) admission and a high 30-day mortality rate [51]. However, several subsequent publications showed that asymptomatic or mildly symptomatic COVID-19 patients with favorable preoperative variables and low ASA (American Society of Anesthesiology) scores could safely undergo surgeries with comparable outcomes to non-COVID-19 patients.

In a published report from a multicenter study of 44 COVID-19 surgical patients (31 (71%) urgent and 16 (36%) major surgeries), 30 days mortality was higher in patients with symptoms (23.1%) compared to those without symptoms (5.6%) [52]. In a large volume New York City hospital report, thirty-nine PCR-confirmed SARS-Cov-2 surgical patients had similar overall ICU admission rates and mortality rates to nonsurgical COVID-19 patients. In addition, COVID-19 patients with ASA score 1 or 2 had a 0% mortality rate in the postoperative period [53]. Another multicenter study, which included 135 confirmed COVID-19 cases receiving general anesthesia, found no significant difference in the rate of postoperative complications in SARS-CoV-2−positive and −negative patient groups, while baseline characteristics strongly impacted these outcomes. Therefore, the authors concluded that SARS-CoV-2 infected patients should be scheduled for urgent surgeries based upon their overall risk of postoperative complication [54].

Recipient's considerations

Outcomes of COVID-19 infection in patients with pre-existing liver disease with high model for end-stage liver disease (MELD) score requiring urgent LT

To date, several studies have evaluated the outcome of COVID-19 infection in patients with pre-existing liver disease; however, characteristics of these patients according to MELD score had not been evaluated separately in these studies. Again an optimal cutoff MELD score to be called High MELD has not been defined. In general, the mortality in patients with a MELD score ≥ 30 is more than 50% at three months. Patients with liver cirrhosis have worse outcomes if they acquire COVID-19 infection. The worse outcome is related to worsening liver condition (MELD score of ≥ 15) and developing respiratory complications.

A report from European Liver and Intestine Association (ELITA) and the European Liver Transplant Registry (ELTR) showed LT candidates with COVID-19 were at high risk of early death (32.7%). The risk of death was 49.2% in patients with decompensated cirrhosis (DC) and Laboratory Model for End-stage Liver Disease (Lab-MELD) score of ≥ 15. The mortality risk is triple when compared with other listed patients with comparable Lab-MELD scores without COVID-19—once recovered from SARS-COV-2 symptomatic infection, the early post-transplant survival was good (96%) [55]. Published results from an International Registry on COVID-19-infected patients with CLD (SECURE-Cirrhosis and COVID-Hep, *n* = 745) reported a much higher mortality rate in COVID-19-infected patients with cirrhosis than in the general population (32% vs. 8%). Mortality in Child-Pugh class A, B, C was 19%, 35%, 51%, respectively, and the leading cause of death was respiratory failure (71%). In addition, 465 had acute hepatic decompensation, and half had ACLF [56].

In summary, a group of patients with ALF, ACLF, and acutely decompensated cirrhosis with high MELD scores constitute sick recipients and warrant urgent LT. However, as of March 2022, after three waves and more than two years of the pandemic, the scope of LT should expand to consider all listed candidates who are likely to benefit from transplantation but are unlikely to receive donor offers due to lower MELD scores or have MELD exceptions or have unsuitable donors. The utilization of SARS-CoV-2−positive liver donors for severely ill patients can be a starting point and can be later expanded to other waitlisted patients with moderate disease.

Why are we scared? Do transplant recipients have a severe infection and worse outcomes if they acquire SARS −COV2 infection, or does immunosuppression confers a higher risk?

There is granular data on outcomes of early COVID-19 infection after LT and the relation of mortality to time since transplantation is

not well established. Several recent studies show that the risk of COVID-19 infection in the early post-transplant period is equivalent to the general population [57]. Moreover, LT recipients with higher age and comorbidities have high mortality. The European Liver and Intestine Transplantation Association (ELITA)/ the European Liver Transplant Registry (ELTR) COVID-19 registry (*n* = 103) has reported that the mortality due to COVID-19 in liver transplant recipients was higher in older vs. younger recipients (22% vs. 0%) and was higher in patients with transplant done more than two years ago than in those who were transplanted within the last two years (18% versus 5%) [58].

We should not change the Immunosuppression (IS) regimen in asymptomatic/mild COVID infection. Tacrolimus-based IS, on the contrary, has shown to be beneficial in SARS-CoV-2 infection as emerging from European Liver Transplant Registry data [59,60] mycophenolate mofetil (MMF) dose should be decreased or stopped if the recipient acquires moderate to severe COVID19 infection [61].

Who should be the recipients of organs from SARS-CoV-2-infected donors: indications of transplantation?

Timely/early liver transplantation from donors with SARS-CoV-2 infection can provide the highest survival benefit to sick patients with high urgency or waitlist mortality. Indications include acute liver failure, acute on chronic liver failure with organ failures, decompensated cirrhosis with high MELD scores (MELD > 25), and select cases of hepatocellular carcinoma [62,63]. Some patients may have minimal matches due to ABO blood group incompatibility (ABOi), inadequate graft to recipient weight ratio (GRWR), poor graft quality, complex liver anatomy, and low remnant liver volume. They can be offered organ as per their waitlist criteria.

Timing of liver transplantation

There have been several published reports of liver transplantation in recently recovered patients from SARS-COV-2. A high MELD score connotes a poor prognosis. Approximately half of the patients with a MELD score of 31−35 and 70% of those with a 40 or more will die within two weeks without a transplant [64]. Many require frequent healthcare visits and hospitalizations and are at increased risk of SARS-CoV-2 infection acquisition and mortality. This risk is much more defined and more in quantity than the risk of SARS-CoV-2 acquisition through transplantation from COVID-positive donors. Patients with decompensated liver failure can have prolonged viral shedding. They may not have the option of waiting as their RT-PCR can remain positive for long periods even after the resolution of infection [9,65−67]. Hence, detection of SARS-CoV-2 by PCR following resolution of symptoms should not discourage the transplant team from considering transplantation. Although LTSI suggests waiting for four weeks after SARS-CoV-2 infections, there are no data to support or refute the timing of liver transplant after SARS-CoV-2 infections [7,68]. Few reports of deceased donor liver transplants 2−70 Days after SARS-COV-2 infections are published [12,24,25,69−71]. A prompt transplantation can improve clinical outcomes if the organ is available from SARS-CoV-2 positive donors. With the paucity of data, the optimal time for transplanting COVID-19 positive patients is not yet precisely clear; However, COVID-19 positive patients with no symptoms/resolution of symptoms and no lung involvement with low CT values at the time of LT should be considered for the transplant.

Serological status of recipients

Transplanting patients with asymptomatic SARS-COV-2 infection with high neutralizing antibody titers due to vaccination or previous SARS−COV2 exposure is a reasonable option for urgent candidates.

However, as we know, patients with chronic liver disease mount a lesser response to vaccines [72], and a growing number of variants may evade the individual's immunity; vaccination status alone does not guarantee protection from a super-infection. Nevertheless, specific studies evaluating the correlation of antibody response and protection against SARS-CoV-2 infection in transplant recipients can confirm the effectiveness of immunization in transplant recipients.

Post-exposure prevention and mitigation strategy

Transplantations are routinely done from donors with blood-borne infectious diseases such as HIV, Hepatitis B, and hepatitis C, as effective therapy is available. The armamentarium to treat COVID-19 today includes (1) Antiviral drugs, (2) Immuno-modulators, (3) Anticytokines, and (4) Monoclonal antibodies. As of the start of 2022, three direct-acting anti-COVID-19 drugs, namely - Molnupiravir, Nirmatrelvir (Paxlovid), and Remdesivir, have received Emergency Use Authorization (EUA). All three agents are potent antivirals and in randomized controlled trials in humans with early COVID-19 who were at high risk for complications, were found to reduce the rate of subsequent hospitalization and death when administered soon after the onset of infection, most reliably if given within five days of onset of symptoms or first identification of infection. Molnupiravir and Paxlovid are administered orally (typically twice daily for five days), while Remdesivir requires intravenous administration (once daily for three days). Remdesivir has received full approval for use in hospitalized patients with severe COVID-19 pneumonia and the need for supplementary oxygen and has become the standard of care in patients with life-threatening COVID-19.

Some of the Anticytokines agents to receive provisional emergency use authorization for treating COVID-19 infection include IL-6 inhibitors such as Sarilumab and Tocilizumab and small molecule inhibitors of JAK kinases, including Baricitinib and Ruxolitinib. In addition, in clinical trials, Dexamethasone has shown convincing evidence of reducing morbidity and mortality in patients with severe COVID-19 pneumonia and respiratory failure and is now recommended only for patients with hypoxia requiring supplemental oxygen or mechanical ventilation.

EUA has been granted to four human monoclonal antibodies in the cock tail regimen, namely, Bamlanivimab with Etesevimab and Casirivimab with Imdevimab, in nonhospitalized patients with early stages of COVID-19 infection. Anti-spike monoclonal antibodies have been associated with good outcomes in solid organ transplantation [73] and utilized post-exposure prophylaxis [74]. A single-center study by Sarrell BA et al. including 93 SOT (50 kidney, 17 liver, 11 lungs, nine heart, and six dual-organ) recipients with mild to moderate COVID-19 who were treated with bamlanivimab or casirivimab-imdevimab showed a reduced risk of emergency department visits or hospitalization for COVID-19, especially in high-risk patients. However, a comparator group of 72 SOT recipients had a higher 30-day hospitalization rate for COVID-19 directed therapy (15.3%) [75]. Dhand et al. described their early experience with the use of casirivimab-imdevimab for treatment of mild-moderate COVID-19 in 25 SOT recipients (17 kidney, two liver, three heart, and two heart/kidney), with multiple other risk factors for progression of disease; none of the patients experienced progression of symptoms or required hospitalization due to COVID-19 [76]. In a study total of 34 COVID positive abdominal organ transplant recipients were administered COVID mAb therapy on an outpatient basis. COVID mAb therapies reduced hospitalization from 32% to 15% (*P* = 0.045) and eliminated mortality (13% versus 0%, *P* = 0.04) [77].

To summarize, the armamentarium to treat COVID-19 has been expanded in 2022 and can mitigate the risks of SARS-CoV-2 donor-derived infection and progression to severe disease post-transplantation. The routine anticoagulation in the post-transplantation period should be continued.

Peri-transplant donor and recipient monitoring

There is scanty literature on how to monitor recipients for transmitted infection. We outline a clinically viable method for monitoring such patients. A routine liver biopsy should be done from liver allograft at transplantation. Post-transplant donors and recipients are placed in appropriate isolation facilities with modified droplet precautions. They are clinically monitored daily for any symptoms or signs for 14 days and initiate proper testing if required. Blood samples for SARS-CoV-2 RT-PCR are assessed on post-transplant 48 h, days 7, 14, 21, and 28. Cultures to detect the viable virus in blood or liver tissue may best identify early infection from the allograft but may not be available. In the peri-transplant period, a protocolized monitoring of nucleocapsid and spike antibodies can assess the durability of serologic status. If the patient is clinically doing well, we may not give routine post-exposure prophylaxis and empiric antiviral treatments. If the recipient acquires SARS-CoV-2 infection, we should determine the viral SARS-CoV-2 strain to identify if the infection was donor- or community-derived. Thus, screening at this site may reflect the new community-acquired acquisition instead of organ-derived SARS-COV-2 infections.

Other considerations

Safety of healthcare workers (HCWs) — the risk of perioperative COVID-19 transmission to the transplant team

When choosing a donor with a potential COVID-19 infection, the risk of transmission puts the recipient and the healthcare providers involved in organ procurement, surgery, and post-transplant care at risk of infection. The risk of COVID-19 transmission to HCWs in the perioperative period depends upon several factors like presence of neutralizing antibodies owing to prior exposure to COVID-19 or vaccination, appropriate usage, and compliance with personal protective equipment (PPE), exposure as measured by the Ct values of the infected patients, measures taken in the operation theater to decrease the exposure, COVID-19 minimal exposure pathways and COVID-19 exposure outside the workplace. Perse, there is scant data on the 'operative' transmission of COVID-19 to HCWs during LT. There is no data if the risk of COVID-19 exposure is more with LDLT surgery versus routine care of COVID-19 infected liver patients or liver organ recipients.

To date, several publications have proven that Healthcare workers constitute a high-risk group for SARS-CoV-2 infection. For example, a recent meta-analysis of 11 studies found that 10.1% of all patients with COVID-19 were SARS-CoV-2-positive HCWs [78].

Also, there are increasing reports of breakthrough infections in a small percentage of vaccine recipients. In a study, SARS-CoV-2 breakthrough infections were documented in 38 of 1497 fully vaccinated health care workers. Most breakthrough cases were mild or asymptomatic and had lower titers of neutralizing antibody and S-specific IgG antibody during the peri-infection period than those in matched uninfected controls. Such candidates may benefit from booster dosage. High-neutralizing antibody titers in peri-infection periods were associated with higher Ct values and lower infectivity [79]. Most of those exposures were outside the workplace. In this study that described the nosocomial outbreak investigation in a transplant unit with SARS-CoV-2 whole-genome sequencing, two likely potential sources of outbreak included staff-to-staff and staff to- patient transmission events. Vaccination rates of the staff in the transplant unit remained well below the hospital average (65.8% vs. 80.1%) [80].

To summarize, SARS-CoV-2 infections among HCWs can go unrecognized. The risk of occupational exposure should be controlled through the proper use and compliance of personal protection equipment and other infection prevention measures. In addition, HCWs, catering transplant units should be mandatorily vaccinated to prevent healthcare-associated COVID-19 outbreaks. Knowing the seroprevalence of SARS-CoV-2 antibodies among HCWs can be a surrogate marker of the extent of the spread of COVID-19 among HCWs and helps assess the success of infection mitigation interventions in the community and healthcare settings. Also, it can help healthcare leaders in considering staff allocations and assignments accordingly.

Hospital resource utilization and logistics

In addition, a medically and surgically complex candidate may strain the resources with prolonged stay in the critical care unit (ICU), large amounts of blood products, subspecialty support, and human resources. Therefore, a healthcare system that typically does not have issues related to shortages of PPE, blood products, ventilators, and ICU beds will be required to conduct such procedures.

Ethics

Transplantation is an essential medical service and should be continued even in difficult COVID times. Liver transplantation during pandemic times should continue to serve three basic principles of transplant benefit: equity, utility, and urgency [81]. When we consider utilizing organs from COVID-positive donors, 'equity' during organ allocation is best maintained; a life-saving opportunity is awarded to recipients with the highest chances of a good outcome and the most significant need for transplantation. It is up to us and the healthcare system to consider taking this risk seriously, as nothing noble comes without danger [82].

Informed consent

We should describe existing steps and precautions adopted by the institution to prevent the spread of infection. In addition, we should explain to all the patients the possible risk of transmission of COVID-19 from donor to recipient and the risk of developing COVID-19 post-transplant from sources not related to the donor or donor organ. We should also explain the natural history and management of SARS-COV-2 infection in transplant recipients. Finally, a shared decision should be taken by choosing to undergo transplantation against choosing to stay on the transplant waitlist.

Conclusion

This review sheds light on several barriers that have so far discouraged SARS-CoV-2 positive donors and recipients from participating in liver transplantation. LT should be considered in asymptomatic or mildly symptomatic SARS-CoV-2 positive, waitlisted patients with end-stage liver disease having neutralizing SARS-CoV-2 antibodies owing to previous COVID exposure and vaccination if the respiratory function is normal. Similarly, mildly symptomatic/ asymptomatic SARS-CoV-2 positive donors can safely donate non-lung solid organs and expand the donor pool. The risks of death while remaining on the transplant waitlist must be judiciously balanced against the risk of SARS-COV-2 transmissions. Currently, the option of vaccination and treatment with monoclonal antibody therapy and remdesivir are available to mitigate SARS-CoV-2 in an exposed transplant recipient and health care workers. While carrying out LT in SARS-CoV-2 infected patients, we must minimize the collateral damage by keeping COVID minimal-exposure pathways in place. A lot has already changed in the current SARS-COV-2 pandemic, and it is now time to change our practice and policy.

Declaration of Competing Interest

The authors have none to declare.

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Dhiraj Agrawal: Writing – original draft, Writing – review & editing. **Sanjiv Saigal:** Writing – original draft, Writing – review & editing.

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