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Editorial

SARS-COV-2 positive donors for liver transplantation – the way forward



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Despite effective vaccination for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) being available for over a year now, the world is still in the midst of a coronavirus disease 2019 (COVID-19) pandemic, without a clear end in sight. In fact, many regions are now seeing surges in cases due to the increase transmissibility in the Omicron variant. As a result, there continues to be disruptions across all medical services to accommodate the increase in admission of COVID-19 patients. In the majority of places, we have observed a redirection of health care resources to manage this influx, of which liver transplantation (LT) has not been left unscathed. The reduction in LT activity has also been contributed by the rejection of organs from SARS-CoV-2 infected donors. There are several main reasons for this. Firstly, there is the risk of transmission of virus to the recipient. Secondly, the outcome of transmission and the development of COVID-19 in a liver recipient is unknown. Thirdly, for living donors who are SAR-Cov-2 positive, there is an additional concern regarding donor safety. Last but not least, there is a risk of transmission to health care professionals, especially for those in the operating theatre for long periods of time.

In the current issue of Journal of Liver Transplantation, Agrawal & Saigal provides a timely and comprehensive review on the use of SARS-CoV-2 positive donors for LT, addressing the key aspects including transmission risk and recipient outcome [1]. Indeed, SARS-CoV-2 infection of the liver has been observed in COVID-19 patients with hepatic impairment, with identification of typical coronavirus particles displaying spike structures being identified in the cytoplasm of infected hepatocytes [2]. Whether these particles are able to replicate and remain infectious is unknown. In addition, these were observed in patients with elevated aminotransferases, which in the first instances, may have already been rejected as a potential donor. From November 2020, deceased donor grafts from active COVID-19 donors were allowed for urgent-need LT in Italy. Report from the first 10 LT showed that testing for SARS-CoV-2 RNA on donor liver biopsies at the time of LT was negative in 100%, which would suggest an extremely low risk of transmission with LT [3]. In addition, evidence presented so far from inadvertent donations from SARS-CoV-2 infected donors showed no evidence of transmission of virus in LT.

For the recipient, the fear of donor-recipient transmission rest on the concern that it may negatively affect the outcome and survival of the recipient. Although LT was observed not to be an independently

associated with increased mortality in SARS-Cov-2 infected patients, it is important to note that these were with respect to stable LT recipients where the median time from LT was 5 years [4]. In essence, these will be quite different to newly transplanted recipients being infected with SARS-Cov-2. In the current review, the authors proposed, and quite rightly so, that those with the highest survival benefit should receive these organs, namely those with high urgency or waitlist mortality, including those with acute liver failure, acute or chronic liver failure with organ failures, and decompensated cirrhosis. These patients are likely to be hospitalised with high MELD score and at high risk of developing pulmonary complications even without SARS-Cov-2 infection. Therefore, it would be fair to assume that the outcome of these sick recipient will be quite different to that of a stable LT recipient several years out from LT. Due to the fact that the transmission rate is negligible to date, the progression of disease and outcome of new infections acquired at the time of LT in liver recipients remains unknown.

It is also important to identify suitable patients that would be safe to accept grafts from SARS-Cov-2 positive donors. One potential group of recipients would those already infected with stable disease. However, the risk of developing COVID-19 pneumonia is high for patients undergoing surgery even if they are asymptomatic, with high post-operative morbidity and mortality rates, possibly as a result of surgery-induced decrease in cell-mediated immunity [5]. Other potential recipients would include those who have recovered from recent SARS-Cov-2 infection protected by natural immunity, and those without prior infection and high levels of neutralizing antibodies from vaccination. However, the optimal timing from recovery to LT and the level of antibody titre deemed protective remains unknown.

After LT using a SAR-Cov-2 positive donor, there are further important considerations. These include the optimal strategies for immunosuppression, disease monitoring, and antiviral treatment. For immunosuppression, although we can extrapolate from existing data about the risk and benefits of different immunosuppressive agents in COVID-19 patients, these are largely derived from stable LT recipients, and not those immediately after LT [6]. For those sick recipients with high MELD scores and extra-hepatic organ impairment, it is likely that immunosuppression will be kept to a minimal in the early post-operative phase. The optimal monitoring

strategy is also unclear. The authors proposed routine liver biopsy at LT, and SARS-CoV-2 RT-PCR testing at regular intervals up to 28 days. Whether further protocol liver biopsies to identify allograft infection are warranted in the absence of graft dysfunction remains debatable especially if the RT-PCR tests are negative. With the recommended RT-PCR testing at regular intervals, these results may have the potential to guide immunosuppression titration and decide whether antiviral treatment against SARS-CoV-2 should be administered. Whether the latter should be offered prophylactically or on the basis of RT-PCR results, and which regimen would offer the best outcome in the immediate post-LT setting remains to be determined.

For living donor LT, the authors proposed that mildly symptomatic/asymptomatic SARS CoV-2 positive donors can undergo donor hepatectomy safely. In this setting, it is not the risk of transmission, but rather the donor safety which is always of paramount importance. Therefore, for this to become acceptable, there needs to be strict criteria rather than using the crude yardstick of defining symptoms as absent/mild. More objective studies including formal lung function test and CT thorax in addition to the routine chest radiograph and oximetry would be warranted. Finally, one must be wary of the well-documented immunosuppressive effect of surgery itself, and the period of immobilisation and reduced respiratory effort post-operatively which may negatively impact the SARS-COV-2 positive donor with increase in chest complications.

Finally, one cannot underestimate the risks posed to the transplant team in operating on an infectious SARS CoV-2 positive patient. The risk of acquiring infection within the small confines of an operating theatre would presumably be high, even though the exact risk is not known. If indeed a transplant surgical team becomes infected, this may jeopardize the LT program, especially in smaller centres, and transplant services may have to be suspended. To minimize this risk, additional implementations such as isolated operating theatres with negative pressure environment will be required. This would be a labour and resource intensive exercise which may appear to be counter-intuitive at a time where services are rationed and redirected at managing COVID-19 patients. However, it is likely that there are already COVID-19 patients requiring emergency surgery and radiological procedures, with the necessary implementations in place already.

It has been more than two years since the start of the pandemic, and with increasing knowledge, our views and approaches to COVID-19 have evolved. With effective vaccination being available, and with milder variants being the predominant strain, the paradigm of SARS-CoV-2 infection has shifted considerably to a point where many regions have adopted the narrative of living with COVID-19. The review on the use of SARS-CoV-2 positive donors by Agrawal & Saigal

is timely and highlights the importance in moving forward in a world where COVID-19 is likely to remain with us for some time. Therefore, it is imperative that we adapt to this new world. Ultimately, the feasibility of using donors with SARS-CoV-2 will depend on regional case-load numbers, resource availability, infrastructures, and policies. This review provides an important framework, emphasizing on the salient key issues that are important in the approach of using SARS-COV-2 positive donors. What is apparent is that there are still many unanswered questions. However, this should not serve as a barrier, but rather as an opportunity to address some of these essential questions, including identifying the optimal types of donors and recipients through specific criteria, and minimization of risk to living donors, recipient, and the transplant team. Given the novelty of the situation, there is still much to be learnt.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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