Liver Transplantation During the COVID-19 Pandemic: Viruses, Vaccines and Beyond

The ongoing COVID-19 pandemic has had unprecedented effects on the care of patients with liver disease owing to a loss of resources, personnel and donors. It led to a glut of communication, in a massive global effort of coordinated scientific collaboration. This was initially led by experts from China and Italy, which saw the first peaks in COVID-19, and has since then been supplemented by various professional bodies on liver disease and liver transplant (LT) across the world.[1–3] Within the field of liver transplantation, a multitude of guidelines have been published with respect to various aspects, the commonest topic being the impact of COVID-19 infection in LT recipients.[2] However, there has also been acknowledgement that different centres have dealt with the pandemic differently.[4] Western literature has also acknowledged the ethical challenges in transplantation during the pandemic, with many centres trying to balance distributive justice, patient autonomy and beneficence on the basis of their individual position on the pandemic curve, as well as the logistic challenges created by a severely depleted intensive care unit (ICU) resource that has been one of the main constraints over a 12-month period.[5]

The article by Soin *et al*[6] highlights these challenges faced in the Indian scenario, where traditionally, the burden of transplantation is carried by live donors. Broadly, it is interesting to note that similar patterns emerge in dealing with donor and recipient management with respect to COVID-19.

General hospital-based measures in the article by Soin *et al*[6] are particularly similar to the measures adopted at our centre in the UK as well. These include minimising footfalls in the hospital by shifting all possible outpatient appointments to virtual consultations, routine screening of healthcare staff and patients, creation of a 'clean' pathway for patients recently screened negative for COVID-19 and strict adherence to mandatory measures such as the use of masks and regular use of hand sanitizers/handwashing. Visiting remains suspended in all hospitals across the UK on the day of writing, with privileges granted only for relatives of patients who are in the palliative setting or those who have complex care needs provided by their relatives (e.g., significant learning difficulties).

In the deceased donor setting, the screening of donors for COVID-19 has been the cornerstone of safety. NHS Blood and Transplant, the regulatory body for transplantation in the UK, recommends at least three negative reverse transcription polymerase chain reaction swabs (one being from an endotracheal aspirate) before being considered for donation. The early opinion was to always refuse organs from those with an acute respiratory syndrome secondary to COVID-19;[7] however, recent evidence has raised the possibility of accepting nonlung solid organs for transplantation based on the fact that RNA viruses have not been isolated in nonlung solid organs and that organs from patients infected with other respiratory RNA viruses are routinely used in transplantation.[7] In the live donor setting, as reported by Soin *et al*,[6] the testing is elective and as close to the donor operation as logistically feasible to ensure safety and protection.

The screening of the liver recipient is slightly more complex, with a few more factors to be taken into account. These include the need for transplantation and the assessments (clinical, biochemical and radiological) that come along with that before considering the actual operation itself. While recipients with an acute COVID-19 syndrome are generally considered unfit for liver transplantation, it has been deemed safe for transplantation to proceed after resolution of the COVID-19–positive status.[8]

Across the first wave of the pandemic, 157 LTs were performed in the UK across seven centres.[9] These were on the back of measures implemented that were not dissimilar to those outlined by Soin *et al*.[6] This was on the background of an 86% reduction in donor activity and 84% reduction in liver transplantation activity. Most were carried out from a prioritised 'clinically urgent' list of patients that was collated nationally and updated regularly.[9] Similar results emerge. Both cohorts had approximately 10% recipients (n = 2/22 in the study by Soin *et al*[6] and n = 15/157 in the study by Thorburn *et al*[9]) who had transplants for acute liver failure. The median Model For End-Stage Liver Disease (MELD) scores were also similar (17.9 in Soin *et al*[6] vs. 18 in Thorburn *et al*[9]), and similar percentages of patients were transplanted for hepatocellular cancer.

Prioritisation of paediatric centres also helped ease the waitlist burden in the UK. This was possible because of the relatively lower COVID-19 disease burden on paediatric ICU settings,[10] where it was possible to protect resources. It allowed some 'small adult recipients' to be transplanted as 'large paediatric recipients'. For example, at our centre, three teenaged recipients underwent whole-liver graft transplantation due to a lack of adult recipients/intensive care capacity.

Abbreviations: MELD: Model for End-Stage Liver Disease; VITT: Vaccine-Induced Thrombosis and Thrombocytopenia

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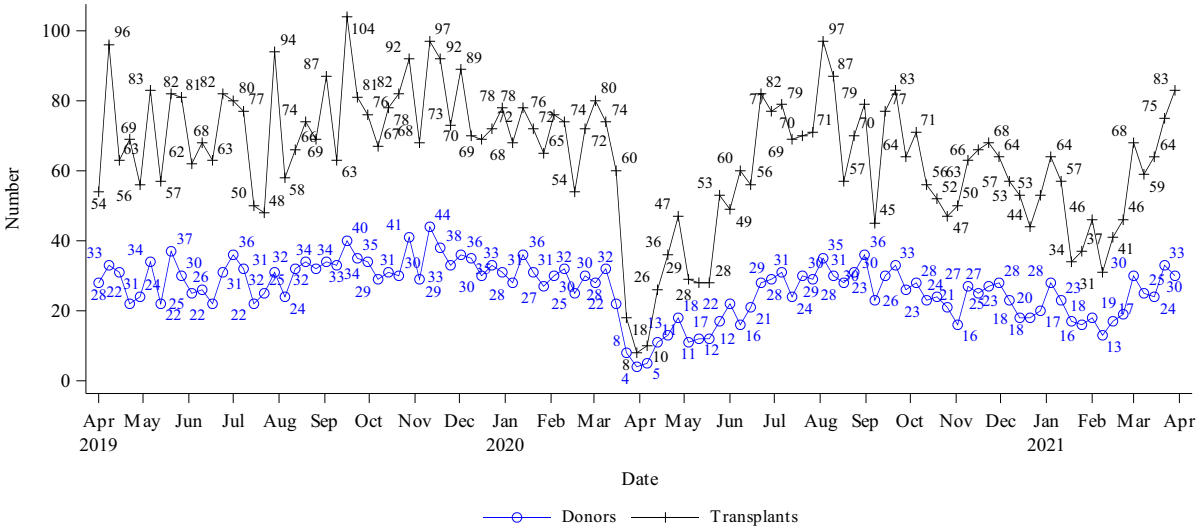

Figure 1 Trend in numbers of deceased donors and corresponding solid organ transplants in the UK since April 2019 (Source: NHSBT ODT clinical[12]).

Other miscellaneous measures worth highlighting include the use of other preservation techniques such as normothermic machine perfusion to allow for prolonged logistic times, in an attempt to overcome delays in ICU resource provision and the use of multivisceral and bowel grafts for paediatric recipients when feasible. Indeed, during the first wave, 31 split LTs and soon after that, five intestinal/multivisceral (liver, pancreas and small bowel) transplants were carried out at our centre.

Scientific collaboration has seen different models emerge to keep transplantation going through the pandemic. Chew *et al*[11] proposed a pragmatic four-dimensional model of 'quadripartite equipoise' to form a balanced framework and guide resource allocation during the pandemic. The four limbs proposed were donor and graft safety, recipient outcomes, waitlist mortality and healthcare resources. The authors noted that as the pandemic waves progressed, there would be a shift in the balance towards and away from liver transplantation based on a calculated 'quadripartite equipoise' score. This was calculated for seven countries across several continents at the time, and the score corresponded with the stage of the pandemic they were in then.

Restoration of near-normal donor activity was reported in the UK in June 2020.[12] By September, Italy and other European countries were in lockdown and the 'UK variant' mutated strain had been discovered. The UK was well and truly in the grip of the second wave by Christmas 2020, when lockdown was announced for the second time. Published evidence is yet to be produced from the longer lasting second wave, however, early indications are that there was amore severe restriction of services in the UK. Several LT centres were closed for adult transplantation for short periods of time, and some patients were transferred to alternative centres to allow them to undergo transplantation. However, a similar precipitous drop in the number of solid organ transplants was not noticed as the deceased donor pathway was maintained (Figure 1).[12] As the pressures on the ICU eased in March 2021, most adult centres were able to undertake transplantation, albeit on a reduced scale compared with prepandemic levels. Transplantation for children continued to remain unaffected during the second wave.

Another evolving piece is on the vaccination front. There are now multiple available vaccines for COVID-19, and are all named differently in different parts of the world. Of interest in this scenario is the AstraZeneca (AZD1222) vaccine. It carries with it a 1-in-1,00,000 risk of developing a syndrome of thrombosis with thrombocytopenia, referred to as vaccine-induced thrombosis and thrombocytopenia (VITT).[13] The syndrome is characterised by thrombosis (most frequently, cerebral venous sinus thrombosis), thrombocytopenia, high D-dimer levels (often along with low fibrinogen levels) and a positive ELISA result for platelet factor 4 (heparin-induced thrombocytopenia test), despite the absence of prior heparin exposure.[12] Among the first reported series (from Germany), four of nine patients had died. As with other immunological conditions, VITT carries a risk of 'passenger lymphocyte syndrome' with it, i.e., the risk of transmitting immune cells that could trigger a similar autoimmune phenomenon in the naive recipient. At present, recipient outcomes are being monitored in the UK, and caution is advised when using organs with high passenger lymphocyte burden, e.g., liver, lung, small bowel and pancreas.

At the time of writing this editorial, India is in the throes of its second wave of the pandemic. There are

reports of shortage of oxygen with heavily overstretched hospital resources, and there is call for international aid on these fronts. The impact of this debilitating second wave in India is likely to have a severe effect on delivery of transplantation services.

It remains to be seen what this pandemic, which has already taken over three million lives over almost 18 months, holds for the future. Liver transplantation has learnt from the first wave as demonstrated by Soin *et al*,[6] and these lessons will be invaluable in shaping care for the long-term future in addition to the immediate remaining duration of the pandemic. It has indeed changed the way we practice medicine.

CONFLICTS OF INTEREST

The authors have none to declare.

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