

# Liver Transplantation in the Time of COVID19: Barriers and Ethical Considerations for Management and Next Steps

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The recent outbreak of the novel virus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes the corona virus disease of 2019 (COVID19), has spread globally and affects millions of people. This pandemic has taxed our health care system and disrupted normal operations, even life-saving procedures, such as liver transplants. During these unprecedented times, providers and patients are imperiled and resources for diagnosis and care may be limited. Continuing to perform resource-intense advanced procedures is challenging, as is caring for patients with end-stage liver disease or patients with urgent needs for liver tumor control. Liver transplantation, in particular, requires critical resources, like blood products and critical care beds, which are fairly limited in the COVID19 pandemic. The potential of COVID19 infections in posttransplant recipients on immunosuppression and staff contacts further adds to the complexity. Therefore, transplant programs must reevaluate the ethicality, feasibility, and safety of performing liver transplants during this pandemic. Herein, we discuss the clinical and ethical challenges posed by performing liver transplants and offer guidance for managing patients with end-stage liver disease during the COVID19 pandemic. (*Hepatology Communications* 2020;4:1242-1256).

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), originally recognized in Wuhan, Hubei Province, China, in December 2019 and the pathogen for the corona virus disease of 2019 (COVID19), has spread globally at an alarming rate.<sup>(1)</sup> To date, there are 6,057,853 confirmed cases of COVID19, with 371,666 deaths, and these numbers continue to rise daily.<sup>(2)</sup> In conjunction with the rising incidence of COVID19 in a community, hospitalization rates and the demand for essential but limited resources dramatically increased.<sup>(3,4)</sup> Hospitals and health care providers tried to prepare for the influx

of critically ill patients with COVID19, but in highly afflicted regions, such as New York City, health care systems were rapidly overwhelmed.<sup>(5)</sup> Although the degree of acute spread of disease was less severe in locations without the population density of New York City, concern for the rapid rise in worldwide communities without adequate measures for disease control as well as concern for a second wave of an even worse spread of infection (given the low percentage of populations that have been exposed and may have immunity to SARS-CoV-2) create great challenges for which we must prepare ourselves.

*Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACS, American College of Surgeons; CDC, Centers for Disease Control and Prevention; COVID19, corona virus disease of 2019; HCC, hepatocellular carcinoma; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; MELD, Model for End-Stage Liver Disease; PPE, personal protective equipment; RRT, renal replacement therapy; SARS-CoV/CoV-2, severe acute respiratory syndrome coronavirus/coronavirus-2.*

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A liver transplant is life saving for patients with decompensated cirrhosis not manageable with medical therapy, patients with acute liver failure, and for selected patients with hepatocellular carcinoma (HCC).<sup>(6)</sup> Currently, there are 12,500 patients on the national waiting list for liver transplant in the United States.<sup>(7)</sup> Before COVID19, overall wait-list mortality was 13.2 per 100-wait-list years, with an even higher rate of mortality for patients  $\geq 65$  years of age.<sup>(8)</sup> Due to the unique logistical needs of liver transplantation, many transplant programs suspended or sharply curtailed transplant activity as local COVID19 cases rose rapidly due to insufficient resources and also for the risk of nosocomial spread outweighing the benefit of performing a liver transplant.<sup>(9)</sup> Based on data from the United Network for Organ Sharing, there was a significant reduction in both living and deceased donor liver transplants, an increase in wait-list inactivation due to COVID19-related issues, and a marked decline in recovery of deceased-donor organs.<sup>(10)</sup> When COVID19 rapidly spread in China causing a scarcity of resources, one transplant center in Hong Kong took a 6-month hiatus from performing liver transplants. During this period, there was a reduction in adherence to follow-up and two deaths on their waiting list.<sup>(11)</sup> Extrapolating from this experience, it is likely that patients in the United States will have similar outcomes, and we should anticipate an increase in “wait-list time to transplant” and wait-list mortality. We therefore must restructure our management of these at-risk patients, using ethical guidance in our decision making to deliver appropriate health care while mitigating the spread and impact of COVID19.

## Liver Transplant Process

Processes for liver transplantation include: (1) candidate evaluation, (2) perioperative transplant care,

(3) immediate posttransplant care, and (4) long-term posttransplant care. Unique challenges created by the current crisis include maintaining safe venues for providing patient care, laboratory and radiological testing, and for procedural interventions, including the transplant operation and patient recovery.

## Ethical Considerations for the Transplant Process

Ethical challenges are inherently tied with candidate prioritization for liver transplantation, but these decisions face a new level of complexity when factors beyond organ availability are considered. The COVID19 pandemic poses such challenges wherein standard protocols may no longer be applicable as location and transport issues, disease burden, local culture, and demographics of the local population must be factored into the decision making. During this pandemic, fundamental ethical pillars of beneficence, nonmaleficence, justice, and autonomy<sup>(12)</sup> can guide programs in ensuring that all patients receive appropriate consideration by the transplant team. We discuss these principles and their individual relevance to the elements of the transplant process and the management of patients on the waiting list for liver transplantation.

## The Transplant Process in the Time of COVID19

### CANDIDATE EVALUATION

#### General Candidate Considerations

Patients in need of liver transplant still need to undergo the appropriate multidisciplinary evaluation

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to be accepted as candidates on the waiting list. While performing evaluations, it is essential that the risk of viral transmission to patients and staff be minimized, thus honoring nonmaleficence. Inpatient and outpatient visits can be modified to minimize patient contact, as recommended by the American Association for the Study of Liver Diseases (AASLD),<sup>(13,14)</sup> and considerations for an in-person examination must take into account the availability of local resources, therefore stressing the role of distributive justice. Some of these considerations are discussed below.

According to the Centers for Disease Control and Prevention (CDC), patients with liver disease are considered at higher risk for severe COVID19 infection.<sup>(15)</sup> Early information from the CDC regarding the underlying medical conditions of 7,162 COVID19 cases showed that 0.6% (n = 41) had chronic liver disease, with 22% requiring hospitalization and 17% of those requiring intensive care unit (ICU) admission.<sup>(16)</sup> Patients with nonalcoholic fatty liver disease may be at a higher risk of severe infection, possibly due to their metabolic comorbidities, including diabetes and obesity, which are known risk factors for severe disease.<sup>(17)</sup> Data from China<sup>(18)</sup> suggest that patients with cirrhosis, and especially those with elevated bilirubin, have increased mortality with COVID19; and new registry data from the United Kingdom and the United States suggest that mortality may increase with the increase in the Child-Pugh score.<sup>(19)</sup> This information reinforces the need to minimize the risk of COVID19 infection in patients before a liver transplant.

## SPECIAL CONSIDERATIONS

### Hepatocellular Carcinoma (HCC)

Patients with HCC on the waiting list or eligible for listing for liver transplant should continue their care due to the risk of tumor progression with delays. To this end, multidisciplinary recipient review committee and tumor board meetings should continue uninterrupted if possible. Although outcomes on COVID19 in patients with HCC are unknown, a recent study evaluating 18 patients with cancer from Wuhan, China, found them at increased risk for severe disease.<sup>(20)</sup> During this COVID19 pandemic in which we are trying to minimize unnecessary patient contact and in-person visitation, risk models and biomarker

panels could stratify those patients at highest risk of HCC development to best prioritize those that need imaging.<sup>(21)</sup> However, these models have not yet been externally validated. Per the European Society of Medical Oncology (ESMO), the highest priority for imaging should be given to those patients with suspected HCC lesions, for assessing tumor treatment response, assessing potential distant metastases, and for patients with hepatic decompensation.<sup>(22)</sup> Although semi-annual surveillance does increase early detection,<sup>(23)</sup> no studies have compared surveillance intervals of 4-8 months, and it is therefore reasonable to delay imaging if needed. A recent study by Rich et al.<sup>(24)</sup> that looked at HCC doubling rates found that the median doubling time was 292 days; however, in 25.1% of patients, doubling time was <90 days along with a longer doubling time in patients with nonviral cirrhosis. Interestingly, rapid growth was seen mostly in smaller tumors whereas larger tumors exhibited more indolent growth. This follows the theory that HCC exhibits sigmoidal growth patterns as larger tumors may begin to outgrow their blood supply.<sup>(24,25)</sup> This raises a slightly challenging scenario, however, in which delay in imaging and identification of these smaller tumors may ultimately preclude future curative options, such as transplant or resection. At the same time, the findings that larger tumors exhibit longer tumor doubling time may argue that treatment can potentially be postponed. For this reason, there should be open discussion with patients with clear documentation of plans, including the risk and benefits of delaying imaging or HCC treatments. Another important factor is that the sensitivity and specificity of screening ultrasound, which is the current recommended imaging modality per various professional societies, remain suboptimal, especially for early lesions.<sup>(26)</sup> Up to 20% of ultrasound studies will be classified as inadequate, and a different imaging modality is required for accurate evaluation of lesions, with about a 5% false-positive rate.<sup>(27,28)</sup> A study by Atiq et al.<sup>(29)</sup> looked at physical harm from HCC surveillance. They defined this as any follow-up testing, including computed tomography or magnetic resonance imaging, liver biopsy, or angiography performed for a false-positive or indeterminate result. They found that over 25% of patients endured physical harm for false-positive results. In this COVID19 era in which we face challenges to obtain imaging and perform treatments, we must be cognizant of the limitations

of our current screening strategies and accept that this may result in further exposure and possible harm to our patients. For this reason, we stress the importance of individual clinical evaluation to decide which patients can safely delay imaging at this time.

The International Liver Cancer Association issued guidelines regarding treatment of HCC during the COVID19 era that reinforced the need for multidisciplinary discussions regarding the need and timing of treatment. These guidelines discussed potential bridging options for all stages of treatment because transplant and resection presents the highest risk for nosocomial infection while also using the most resources (operating room, critical care bed, and blood products). ESMO denotes patients with high priority for intervention as those listed for transplant with HCC with either acute or chronic liver failure, high Model for End-Stage Liver Disease (MELD) score, or with tumor burden nearing the upper limit of Milan criteria as well as patients in which curative surgery is an option for large or multifocal lesions.<sup>(22)</sup> As ~10.5% of wait-listed patients have a primary diagnosis of HCC and a third of all transplants are performed for this indication,<sup>(8)</sup> identifying which candidates can safely delay transplant is critical. Mehta et al.<sup>(30)</sup> evaluated patients with HCC on the transplant list and noted an overall dropout rate of 15.1%. Those with a single lesion (2-3 cm), Child-Pugh A, MELD score <15, and alpha-fetoprotein <20 predicted lower risk for dropout, and therefore these criteria may guide identification of patients in whom transplant can be delayed. Lastly, for patients on systemic therapy, it has been recommended that oral tyrosine kinase inhibitors are preferred over infusion-based regimens to minimize nosocomial exposures.<sup>(31)</sup>

## Other MELD Exceptions

Patients with portopulmonary and hepatopulmonary disease with MELD score exceptions on the waiting list deserve additional mention. Those with hepatopulmonary disease are likely to be at increased risk for severe pulmonary complications if they contract COVID19 and thus potentially overuse critical care resources. Similarly, patients with portopulmonary syndrome require infusion-based vasodilators to control pulmonary hypertension; this potentially extends their stay in the ICU and overuses strained

resources, posing additional challenges, including discharge disposition.

## CANDIDATE MANGEMENT

### Inpatient Care and Hospital Transfers

Care for actively listed patients with complex medical problems should continue in the hospital with modifications to reduce contact and minimize the risk of acquiring COVID19. If feasible, certain physician visits may be conducted virtually. Additionally, hospital policies must restrict patient caregiver and family presence in the hospital to reduce the risk of COVID19 transmission.

It is recommended that policies for triage and review of patient transfers be developed. Only those patients active on the transplant list or who are in need of interventions that are currently being performed solely at the transplant center should be accepted.<sup>(13)</sup> Transfers and evaluation of potential transplant candidates with low MELD scores and no urgent need for transplant listing can be temporarily deferred and potentially moved to the outpatient setting at a later date.

### Outpatient Care

Outpatient visits should be limited to essential visits.<sup>(32)</sup> Conditions requiring in-person evaluation include new onset jaundice, aminotransferase levels of >500 U/L, or new hepatic decompensation.<sup>(13)</sup> Before the encounter, patients should be screened for symptoms of and recent exposure to COVID19, both the day before and on the day of the visit. Temperature checks before entering the clinic area should be performed; however, individuals may have asymptomatic COVID19 infections, complicating current screening without formal testing. Should there be a concern that a patient is infected, they should be seen in a dedicated COVID19 space.

Outpatient facilities should strive to limit the number of patients present at a given time by staggering arrival times and limiting the accompanying friends or family members. A minimum number of health care providers should partake in the visit and appropriate personal protective equipment (PPE) provided to patients and staff.<sup>(13,32)</sup> Telehealth visits and local laboratory testing should be encouraged. It is noted that telehealth has various barriers in regards

to the delivery of care. There are currently restrictions regarding telehealth care across state lines; this disadvantages patients that are in regions without local availability of advanced hepatology care.<sup>(33)</sup> While some transplant programs had established infrastructure to deliver telehealth in the pre-COVID19 era, many programs did not due to regulatory and/or reimbursement limitations. Therefore, a nationwide discrepancy remains in the ability to successfully implement these programs at an equivalent rate.<sup>(34)</sup> We must also be cognizant that certain demographics, such as the elderly or lower socioeconomic strata, may lack access to equipment or to the internet and have limited technological proficiency to engage in telehealth-delivered care. We must continue to engage, motivate, and offer clear and directed instructions to these patient populations during this time. On March 6, 2020, the Coronavirus Preparedness and Response Supplemental Appropriations Act (H.R. 6074) was passed and temporarily lifted certain Centers for Medicare and Medicaid Services (CMS) restrictions regarding telehealth care.<sup>(35)</sup> Although this has helped deliver care, it is uncertain how long this will remain in effect, and rules for licensure are determined at the state level. Therefore, we must understand the limitations that alter access for certain patients and offer remediation to improve patient access to telehealth care.

The Organ Procurement and Transplantation Network recently updated their policy (Policy 1.4.F) to allow transplant centers to use previous clinical data to maintain wait-list priority in situations where repeat testing is not feasible due to the COVID19 crisis.<sup>(36)</sup> Vaccinations for *Streptococcus pneumoniae* and influenza should be updated. Endoscopic variceal screening should only be performed for high-risk patients, including those with a recent bleed or with high-risk stigmata.<sup>(37)</sup> Noninvasive risk assessment, including the Baveno IV criteria, should be applied to risk stratify patients, and if tolerated, beta-blockers should be used empirically for high-risk patients.<sup>(14,38,39)</sup>

## Ethical Considerations for Candidate Evaluation and Management

Ethically speaking, candidate evaluation and management in the COVID19 pandemic requires balancing of beneficence with nonmaleficence. Such a balance may favor beneficence over minimized harm

for a high-risk patient, i.e., high MELD score, acute liver failure, status 1A patient, among others, who are set to gain the highest survival benefit from an early liver transplant, thereby accepting the risk of COVID19 exposure, i.e., minimized harm, during the evaluation phase. Whereas in low-risk patients, i.e., whose outcomes are not time critical, nonmaleficence may outweigh beneficence whereby exposure to COVID19 to this subset of patients may do harm for their candidacy for liver transplant. Furthermore, in the latter group of patients, the principle of distributive justice must also be respected; consideration directed to not unduly strain and diverge the critical resources (e.g., PPE kits, health care worker staffing) is essential in overcoming the COVID19 pandemic.

## Liver Transplant Candidate Triage

Once a program determines it has the adequate resources to perform a liver transplant and has adequate COVID19 testing protocols in place, it then triages which wait-listed patient would be most suited to undergo a liver transplant. Under nonpandemic circumstances, the triage of liver transplant is based on medical need, which is driven by the MELD score. During the COVID19 pandemic, the need-based triage is altered to “disaster triage,” which follows the principles of distributive justice and thus adds clinical and ethical complexity in the decision to perform a liver transplant.

The National Confidential Enquiry into Patient Outcome and Death triage system allocates surgery into immediate, urgent, expedited, and elective categories.<sup>(40)</sup> Liver transplant surgery tends to combine the latter two into one, i.e., elective, and that category usually represents adult living-donor liver transplants. Deceased-donor liver transplants, however, encompass all the aforementioned categories and therefore require urgent triage given the expeditious and critical nature of the procedure. Notably, CMS currently classifies transplant surgery as a tier 3b procedure and therefore not an elective surgery.<sup>(41)</sup> In this direction, surgical societies, such as the American College of Surgeons (ACS) and specifically the American Society of Transplant Surgeons (ASTS) and British Transplantation Society, formulated guidance documents to facilitate decision making for transplant surgeons.<sup>(42-44)</sup> The guidance illustrates that elective surgery, like living-donor liver transplants, be

postponed (assuming the recipient can wait). This is because the double equipoise of living donation, which seeks to balance donor risk with recipient benefit, is compromised. For deceased-donor liver transplants, the transplant team must be cautious and critically evaluate each organ offer for the specific recipient in light of resource availability, impact of immunosuppression, and presence of a robust convalescence plan.

Kumar et al.<sup>(45)</sup> outlined a tiered approach in which to consider liver transplantation (Table 1). By breaking down transplant activity from 0%, in which a health care system is completely overwhelmed and unable to

provide any surgery, to 100% availability, we can recommend phases in which candidates should be considered. Phase 1 (25% program availability) would be emergent cases only for immediately life-threatening conditions, e.g., acute liver failure, MELD score >30. Phase 2 (50% program availability) would be urgent cases, including patients who can defer services for a period of 14 days but not for the expected length of the pandemic, e.g., MELD score >25, no living-donor activity for stable recipients. Phase 3 (75% program availability) would be elective cases, including patients without life-threatening conditions who can

**TABLE 1. TIERED APPROACH TO TRANSPLANT SURGERY DURING COVID19 SHOWING THE DEGREE OF REDUCTION NECESSARY IN TRANSPLANT ACTIVITY AS GOVERNED BY RESOURCES AND ETHICAL PRINCIPLES IN DECISION MAKING**

Surgical Activity	Surgical Priority	Potential Surgical Candidates	Major Ethical Pillars
Tier 1 (0% capacity) complete	No transplant cases	<ul style="list-style-type: none"> <li>No deceased-donor or living-donor transplants given lack of resources</li> <li>Consider transfer to alternative center for emergent cases</li> </ul>	Justice
Tier 2 (25% capacity) severe reduction	Emergent: <ul style="list-style-type: none"> <li>Life-threatening cases</li> <li>Patient unlikely to survive without intervention</li> </ul>	Considerations <ul style="list-style-type: none"> <li>Acute liver failure</li> <li>MELD score &gt;30</li> </ul> Avoid: <ul style="list-style-type: none"> <li>Living-donor activity</li> <li>Surgical treatment for HCC</li> </ul>	Justice, beneficence
Tier 3 (50% capacity) moderate reduction	Urgent: <ul style="list-style-type: none"> <li>Not immediately life threatening</li> <li>May not be able to manage in outpatient setting</li> <li>Unlikely to survive duration of pandemic without intervention</li> </ul>	Considerations: <ul style="list-style-type: none"> <li>MELD score &gt;25</li> <li>HCC: Surgical treatment for ACLF, high MELD score, nearing upper limit of Milan criteria, large/multifocal lesion still surgically manageable</li> </ul> Avoid: <ul style="list-style-type: none"> <li>Living-donor activity unless unstable recipient</li> <li>Surgical treatment for HCC unless stated above</li> <li>Potential deferral for patients with portopulmonary/hepatopulmonary syndrome or high risk comorbidities per CDC*</li> </ul>	Nonmaleficence Beneficence Justice Autonomy
Tier 4 (75% capacity) mild reduction	Elective: <ul style="list-style-type: none"> <li>No life-threatening cases</li> <li>Can be managed as outpatient with medical therapy</li> <li>Patient condition likely to remain stable for duration of pandemic</li> </ul>	Considerations: <ul style="list-style-type: none"> <li>Deceased-donor transplant</li> <li>Curative treatment for HCC</li> </ul> Avoid: <ul style="list-style-type: none"> <li>Living-donor activity unless unstable recipient</li> <li>Potential deferral for patients with portopulmonary/hepatopulmonary syndrome or high-risk comorbidities per CDC*</li> </ul>	Nonmaleficence Beneficence Autonomy Justice

\*Per CDC, high-risk conditions include asthma, chronic lung disease, diabetes, serious heart conditions, chronic kidney disease, severe obesity (body mass index >40), age >65 years, nursing home/long-term care facilities, immunocompromised patients, liver disease.<sup>(15)</sup>  
Abbreviation: ACLF, acute on chronic liver failure.

be medically managed and for whom services can be deferred for the duration of the pandemic, e.g., no living-donor activity for stable recipients.

Using the principles of beneficence and nonmaleficence, we need to balance those that would have maximal benefit with minimal risk. This changed approach may appear to conflict with the fairness principle of justice, but given the temporary nature of the deferral and also the communitarian approach, it ultimately upholds the “greatest happiness principle” of Jeremy Bentham, the founder of modern utilitarianism.<sup>(46)</sup>

With this guidance, we should therefore consider available resources and local COVID19 prevalence. The ACS along with the American Society of Anesthesiologists, Association of periOperative Registered Nurses, and American Hospital Association have provided a roadmap for resuming surgical activity.<sup>(47,48)</sup> Their recommended stepwise evaluation is useful to help individual programs assess their capacity to deliver safe and effective surgical care and to understand the level of surgical triage they are able to accommodate. During this pandemic, these triage decisions must balance the survival benefit offered from liver transplant against the potential for COVID19 infection in patients, health care providers, and families and primary care givers responsible for posttransplant care.

## PROGRAM ASSESSMENT

### Evaluation of the Transplant Center

Transplant centers must individually determine their ability to safely perform liver transplants. Daily considerations to available resources (blood product availability, access to operating rooms, and critical care beds), adequate health care workers to provide transplant care (medical team, surgical team, critical care team, and nursing ancillary staff), and the relative volume and local prevalence of patients with COVID19 (total patients admitted, discharged, in ICU, and on ventilators) are important.

In determining a program's ability to remain active, justice is the most important guiding principle. As outlined by Emanuel et al.,<sup>(49)</sup> pandemics place excessive demand on and subsequently overwhelm the health care system. This creates the ethical challenge of rationing medical equipment and interventions. As mentioned, liver transplant requires the utilization of

a variety of strained resources. Certain highly afflicted regions are currently not able to offer transplants given the lack of assurance that high-quality critical care and the necessary resources are available. Travel bans and restrictions along with inadequate and inaccurate COVID19 testing has led to challenges and reductions in organ procurement.<sup>(45)</sup> The principle of distributive justice in choosing how to ration the available resources may be the most challenging. We are forced to decide whether or not we can safely and effectively provide a transplant to patients in need of a liver transplant to survive or are best to defer transplantation and allow available organs to go to another center where resources may be more favorable and a better outcome possible.

## PATIENT AND PROVIDER SCREENING

Currently, we do not know the true risk of transmitting the SARS-CoV-2 virus through organ transplantation. Given that SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in bile duct cells, and prior data show the 2003 SARS-CoV virus in the liver as detected by polymerase chain reaction, we assume that transmission is likely.<sup>(50,51)</sup> One case series reported that up to 15% of patients with COVID19 had detectable circulating viral RNA.<sup>(52)</sup> Therefore, the majority of organ procurement organizations and transplant societies are recommending that donors undergo COVID19 screening and those who test positive for COVID19 be deemed medically ineligible for donation.<sup>(42,53,54)</sup> The American Society of Transplantation Infectious Diseases Community of Practice notes that if a donor recovered from a COVID19 infection >28 days ago, had resolution of symptoms, and is negative on repeat testing, their donated organs are likely safe to use.<sup>(54)</sup>

All recipients should undergo testing, and if they test positive for SARS-CoV-2, their transplant should be delayed, if possible.<sup>(13,38)</sup> We must be aware that COVID19 testing by nasopharyngeal sampling has fairly low sensitivity (56%-83%), and thus negative results, especially if inconsistent with clinical history, should be interpreted with caution.<sup>(55,56)</sup> Although there are other sampling sites, including oropharyngeal and saliva samples, that can be used for testing, the Infectious Diseases Society

of America (IDSA) recommends nasopharyngeal testing for symptomatic patients as this sampling site has higher sensitivity. Additionally, although lower respiratory tract samples, including sputum and bronchoalveolar lavage, have better sensitivity, the IDSA only recommends this type of sampling if the upper respiratory testing is negative and if there is a high clinical suspicion.<sup>(57)</sup> Lastly, there are also a variety of serologic tests available for detection of SARS-CoV-2 antibodies, with the CDC's enzyme-linked immunosorbent assay-based test showing greater than 99% specificity and 96% sensitivity. However, given the uncertainty of how to interpret these tests with respect to transmissibility or protective immunity, the CDC and IDSA are not recommending this form of testing for diagnosis or important policy decisions.<sup>(58,59)</sup> Patients who test positive for SARS-CoV-2 or have suspicious clinical history or symptomatology or receive an organ from a potential COVID19-positive donor should be placed under contact and airborne isolation and providers should follow the recommended (local and/or CDC) personal protective precautions.<sup>(54)</sup>

Given the significant risk of nosocomial spread, health care workers must be monitored for development of potential infection. In Italy, up to 20% of health care workers became infected with COVID19 while caring for positive patients.<sup>(60)</sup> Another striking review from a single-center case series in Wuhan, China, estimated that 41% of their 138 cases were hospital-related transmissions.<sup>(61)</sup> The Systems Engineering Initiative for Patient Safety is a human factors-based model that assesses the impact of a work system on outcomes. Hoe Gan et al.<sup>(62)</sup> used this model to create a system to prevent health care workers from infection. They recommended segregating health care teams caring for suspected and confirmed patients with COVID19 from managing other patients to minimize cross-infection. They recommended appropriate PPE based on risk stratification of tasks, twice daily temperature monitoring of health care providers, and further testing for fevers or other symptom development. Additionally, recommendations included minimizing patient-provider interactions, reducing the number of team members needed in the hospital, and number of providers entering a patient's room.<sup>(14)</sup>

## Perioperative Transplant Care

### PREOPERATIVE PHASE

Special consideration needs to be given to COVID19 history and/or exposure of the donor and recipient in the immediate preoperative period. We therefore recommend the following before surgery: (1) Update blood bank antibody screening for the recipient and review the local availability of appropriate blood products; (2) assess if the recipient demonstrates signs or symptoms of COVID19 or was exposed to someone with signs or symptoms of COVID19; (3) perform COVID19 testing before surgery on the donor and the recipient; (4) perform chest radiograph of the recipient to ascertain baseline; (5) obtain appropriate informed consent.

Donor selection is guided by the principles of non-maleficence, autonomy, and justice. Although the risk of donor SARS-CoV-2 transmission is not known, we must proceed with the assumption that it exists. When choosing a donor with potential COVID19 infection based on test or history/symptoms, the risk of transmission puts the organ procurement members, the health care providers involved in the surgery, and posttransplant care and recipient at risk of infection. Given the unknown outcomes in immunosuppressed patients infected with COVID19 and knowing that viral shedding may be prolonged,<sup>(63)</sup> infection in recipients could lead to disease transmission or even a potentially lethal outcome. In addition, given the lack of evidence-based data on outcomes of certain experimental COVID19 treatments in our patient population undergoing transplantation, we may ultimately cause more harm if the treatment is administered. It is for this reason that many organs are being declined when donor COVID19 testing is not readily available, especially organs recovered from high-incidence areas or where donor illness or exposure raises concern for COVID19. For living donation, in addition to the standard surgical risks living donors accept, the risk of nosocomial COVID19 infection has led many programs to temporarily suspend living-donation programs for liver transplant.<sup>(13,42,54,64)</sup>

Considering the principle of justice and many marginal or extended criteria, deceased donors may be



declined due to concerns for worse patient outcomes and need for prolonged hospitalization and resource utilization in a resource-strained pandemic environment. However, we know that organs are a precious and scarce resource themselves, and end-stage liver disease carries a predicted high short-term mortality as the MELD score increases. Therefore, deciding not to transplant an organ that may prevent patient demise compromises the pillar of beneficence along with justice. Although such decisions are made at the programmatic level, discussion and appropriate education of patients will help maintain their autonomy, albeit limited.

Recipient selection is guided by the four ethical pillars of the Principlism Theory.<sup>(65)</sup> In regards to “beneficence,” liver transplant is life saving and the gold-standard treatment for patients with decompensated cirrhosis, acute liver failure, and in selected cases HCC.<sup>(6)</sup> In addition, after a successful liver transplant, there exists the possibility that recurrent hospitalizations or frequent clinic visits from complications of liver disease may be avoided, thus reducing the risk of COVID19 infection. The principle of “nonmaleficence” helps guide the balance of risk and benefit when deciding who should undergo liver transplant in this pandemic. Patients for whom emergent liver transplant is not indicated, patients who have certain high-risk comorbidities,<sup>(15)</sup> and patients who are at higher risk of developing severe COVID19 may outweigh the benefits of a transplant during this time. Alternatively, those with emergent indications, such as acute liver failure with its highest survival benefit from a timely liver transplant, have a favorable balance to the benefit versus risk of a COVID19 infection during their posttransplant phase. In regard to “justice,” certain programs may approach transplant candidates by viewing those that would have the maximum benefit by using the least amount of resources. Patients with severe portal hypertension and or redo liver transplant candidates with anticipated higher needs of blood products or those with isolated pulmonary complications that may require extended ICU care may not be best suited for a transplant during this time if the transplant can be safely delayed. However, if programs expect to only offer a minimal number of liver transplants, perhaps only the emergent patients with the highest survival benefit should be accepted, despite their risk of a more complex hospitalization.

Finally, with respect to “autonomy,” our lack of knowledge of COVID19 risk and outcomes make our ability to inform patients on potential complications difficult. Additionally, due to the dynamicity associated with the COVID19 crisis and the public health emergency it has created, decisions regarding selective liver transplant activity and its triage are made at the local programmatic level in a communitarian spirit, and therefore patient autonomy is at risk. However, such is the state of affairs according to the Model State Emergency Health Powers Act that came into force after the terrorist attacks of 2001, making provision for the facilitation of systematic planning in response to a public health emergency.<sup>(66)</sup> However, communitarian policies need not conflict with autonomy as the emerged concept of “responsive communitarianism” seeks to balance autonomy with common good without *a priori* privileging either of the two.<sup>(67)</sup> Thus, adequate education of a patient’s unknown yet probably severe impact of COVID19 infection will help provide the needed balance between social justice and individual autonomy.

## INFORMED CONSENT

Informed consent has its roots in the twentieth century, wherein the English common law tort doctrine of negligence was applied to the field of surgery for patient-centered care.<sup>(68)</sup> It required adequate and pertinent information for the patient to classify the consent as “informed.” Organ transplant societies have recognized the limitations of the informed consent process in the current pandemic because we lack data regarding blood-borne transmission of COVID19 from donor to recipient, its impact when compared to droplet transmission, and impact of immunosuppression on COVID19 severity. Nevertheless, appropriate consenting of the recipient receiving a transplant during a COVID19 pandemic is essential and should include the following<sup>(69,70)</sup>:

- Risk of transmission of COVID19 from donor to recipient. This should be done in the wake of donor test results given the high rate of false negativity and also the presence of asymptomatic patients with COVID19.
- Risk of developing COVID19 posttransplant from sources not related to the donor or donor organ.

- Logistical and organization issues, i.e., availability of blood and its component products, access to operating rooms, critical care beds, and readmission pathways.

For living donors undergoing living-liver donation, besides the standard risks, the donor should also be counseled for the risk of COVID19 transmission during the donation period.

## INTRAOPERATIVE PHASE

It is essential that only the necessary staff participate in the surgery with omission of any observers to minimize transmission. If the patient tests positive for COVID19 or has symptoms and signs highly suggestive of infection, then the surgery should be scheduled in a dedicated COVID19 operating room with negative pressure. Surgical and anesthesiology teams should preferably wear well-fitting N95 masks and face shields. The intraoperative phase is discussed in the next two sections.

### Anesthesia

Aerosolization and droplet transmission of the COVID19 virus are important hazards, the risk of which increases with procedures, such as endotracheal intubation and tracheostomy. Surgeons and personnel not needed for intubation should remain outside the operating room until anesthesia induction and intubation are completed for patients with or suspected of having COVID19 infection.<sup>(71)</sup> The airway should be secured using the method with the highest chance of first-time success to avoid repeated instrumentation of the airway, including using a video-laryngoscope.<sup>(70)</sup> Negative pressure operating rooms and/or anterooms when available are recommended.

### Surgery

Surgical teams should preferably use N95 masks and avoid rescrubbing to save PPE and minimize transmission. The ACS<sup>(71)</sup> and Society of American Gastrointestinal and Endoscopic Surgeons<sup>(69)</sup> recommend that electrocautery be set to the lowest possible setting and used with smoke evacuators, preferably monopolar diathermy pencil with attached smoke evacuator if available.<sup>(72)</sup> There should be

particular attention to blood product use, and if available and clinically feasible, cell-saver should be used to conserve blood. Surgical equipment used for patients suspected of being COVID19 positive should be cleaned separately from other surgical equipment.<sup>(69)</sup> Need for renal replacement therapy (RRT) should be ascertained early on as it may require advanced planning for adequate staffing, especially when RRT utilization is high for patients with COVID19 in the ICU.<sup>(73)</sup>

## POSTOPERATIVE PHASE

Patients for liver transplant are routinely monitored in a higher acuity unit (ICU, surgical high-dependency unit). Given the abrupt and large influx of critically ill patients due to COVID19, bed availability should be closely monitored both in COVID and non-COVID units. As the curve of the pandemic flattens and hospitals return to their normal structure, patients from “temporary” ICU locations created during the crisis will need to move back to “traditional” critical care units, creating a further backlog of bed availability. As we expect to selectively perform only high-risk liver transplants (with highest survival probability), prolonged intubation, pressor requirements, need for recurrent transfusions, and RRT may prolong ICU stay.<sup>(15,16)</sup>

Transport of patients from the operating room to the ICU also requires careful planning and monitoring, including ventilator disconnect. The minimum number of transport personnel should be considered and appropriate PPE as recommended by the CDC donned. PPE used should not be the same as used during the surgery,<sup>(71)</sup> and frequent hand washing, cleaning of cell phones, and adequate social distancing should be practiced. COVID locations should be separate from non-COVID locations, and if possible, staffing of designated areas should remain strictly separate.

Ethical considerations during the intraoperative phase are similar to the postoperative phase in that they are simpler because the difficult triaging decision to transplant occurs in the preoperative phase yet they are complex because critical resources are at risk of rapid overconsumption.

The most important ethical tenet in both the intraoperative and postoperative phase in the COVID19 pandemic is that of distributive justice because the

liver transplant procedure and management of critically ill patients with COVID19 exert competing strains on critical resources. Therefore, maximal effort is needed for conservation of critical resources so that the potential needs of 1 patient does not pose a threat to the welfare of many. In addition, limiting overconsumption of resources, such as blood products, PPE equipment, and staffing, particularly of the anesthesia/critical care workforce among others is a morally burdened decision. Thus, the ethical principle of justice is at the center stage in all decisions of the intraoperative and postoperative phase.

Nonmaleficence ranks as the second most important ethical pillar whereby there is a strong focus on reducing COVID19 transmission to both the patient and to health care workers. This is achieved by adequate testing of the patient and health care workers, providing “COVID19 minimal” care pathways, appropriate and recommended PPE, and minimized cross-infection.

## DISCHARGE PLANNING

Destination and level of support needed after discharge should be discussed fairly early in the process to minimize the stay in hospital. Often patients receiving a liver transplant are deconditioned due to cirrhosis and require significant rehabilitation to allow for safe discharge back home. As rehabilitation facilities and nursing homes are hotbeds for COVID19 transmission, early physical therapy and nutrition should be emphasized to increase the safety and success of discharge home. Occasionally liver transplant recipients may need dialysis in the short term. As many dialysis units are overwhelmed, transplant centers should aim to engage dialysis units early on for a seamless transition.

## Immediate Posttransplant Care

The immediate posttransplant period (0-3 months posttransplant) begins from the day of discharge. During this time period, the main focus will be on balancing nonmaleficence with beneficence, trying to avoid unnecessary exposure and risk for COVID19 infection while ensuring appropriate care is delivered. Each program has specific protocols for outpatient

evaluation and monitoring, but common elements include frequent blood draws and clinic visits for examination and wound care if needed. In this current pandemic, it is reasonable to space out in-person visits, although these decisions need to be made on an individual and programmatic level and based on the complexity of the postoperative course. When in-person visits are needed, the aforementioned precautions should be implemented. Additionally, a portion of these patients could require readmission within 30-days of discharge, and in some regions this has been as high as 50.8%.<sup>(74,75)</sup>

## IMMUNOSUPPRESSION MANAGEMENT

While other viral infections, such as adenovirus, influenza, and rhinovirus, tend to cause more severe infections in patients who are immunosuppressed, data on other coronavirus infections (including SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]) do not follow this pattern.<sup>(76-79)</sup> Although we lack long-term data on the impact of immunosuppression in transplant recipients in the COVID19 pandemic, it is generally considered appropriate to initiate and is safe in the short term.<sup>(80)</sup> Maintenance immunosuppression generally consists of tapered steroids followed by a calcineurin inhibitor without or with an antimetabolite.<sup>(6)</sup>

The limited data on the use of immunosuppression after a liver transplant in patients who are COVID19 positive are based on experience from various centers, and thus far it does not appear that patients on immunosuppression have a more severe disease course. For example, in Lombardy, Italy, where over 25,000 COVID19 infections have been confirmed, Bhoori et al.<sup>(81)</sup> reported outcomes on their liver transplant recipients. From their long-term posttransplant cohort (>10 years out), they noted that 3/111 died following COVID19 infection. Each of these patients was on monotherapy with a low-dose calcineurin inhibitor, and all were men, age >65 years, overweight (body mass index >28 kg/m<sup>2</sup>), on antihypertensive agents, and had diabetes. Notably, the CDC views these demographics and medical conditions as high risk for severe illness from COVID19 infection.<sup>(15)</sup> In their recent cohort of patients receiving a transplant (within 2 years),<sup>(81)</sup> 3 out of 40 had COVID19 infection and all had mild course without the need for hospitalization. Thus, a conclusion

can be derived that immunosuppression does not seem to increase the risk of severe COVID19 as the mortality rate in their cohort was 3% compared to the 10% case-fatality rate for the rest of Italy. We do, however, lack data on the risk profile of the 3 patients who were infected and the long-term impact. Another case series from the main pediatric liver transplant center in Italy found no increased risk of severe pulmonary disease after evaluating around 200 patients, including patients with cirrhosis, patients who had received a transplant, patients with autoimmune liver disease, and patients on chemotherapy for hepatoblastoma. Of this group, 3 were confirmed to have positive SARS-CoV-2 infection, although it was felt this was likely underestimated given the reported high prevalence in their population.<sup>(80)</sup>

Due to this initial data and the emerging evidence that suggests the innate immune response is the main driver of lung tissue damage,<sup>(82)</sup> current guidelines do not recommend reducing or stopping immunosuppression in an asymptomatic liver transplant recipient.<sup>(14,38)</sup>

Although we have learned that immune dysregulation and inflammation are the potential drivers for pulmonary deterioration in patients who develop severe COVID19, current guidelines from the IDSA do not recommend use of high-dose steroids unless needed for another therapeutic purpose.<sup>(83)</sup> Initial therapy and an early episode of acute cellular rejection would warrant use of high-dose steroids; however, whether steroid-free regimens should be considered and current protocols for treating rejection modified to reduce steroid exposure is uncertain given the lack of controlled data. Currently, the AASLD recommends that patients with COVID who are immunosuppressed should minimize the dose of high-dose prednisone, reduce azathioprine or mycophenolate dosages, and reduce but not stop calcineurin inhibitors when lymphopenia, fever, or worsening pneumonia is present. In patients with COVID who need modification of immunosuppression, such as those with graft rejection or an autoimmune flare, treatment should proceed with close monitoring.<sup>(13)</sup>

## Long-Term Posttransplant Care

Long-term follow-up in the outpatient setting is important to optimize recipient outcomes. The

majority of patients following liver transplantation require life-long maintenance immunosuppression, placing them at risk for more frequent and possibly more severe infections.<sup>(84,85)</sup> Additionally, transplant recipients with viral illness have shown prolonged viral shedding times, making them potential “super-spreaders” throughout the health care system and their community.<sup>(63,79)</sup> Despite these potential risks, and as previously stated, the current guidelines do not recommend changing immunosuppression regimens prophylactically.<sup>(14)</sup>

The rapid transition to incorporate telehealth into the care paradigm during this pandemic will likely be a permanent part of long-term care for patients, especially as concerns regarding COVID19 may very well continue into the indefinite future. Prior use of telemedicine in patients with advanced liver disease has demonstrated that this form of health care results in expedited transplant evaluations and more efficient triage of patients who are not transplant candidates.<sup>(86,87)</sup> The prolonged future use of telemedicine will also offer advanced hepatologic care to certain disadvantaged patients far from expert care, hopefully helping to resolve some disparities in quality and access to care.<sup>(88)</sup> Using local laboratories and providers as part of the care team along with the transplant center was part of the prepandemic care model and will be even more important in the future. However, the pandemic has also disrupted many primary care practices, and transplant centers may have to assist patients with care beyond immunosuppressive management to fill gaps in our patients’ needs until a new equilibrium is restored in the community.

The ethical considerations of posttransplant care both in the immediate and long-term focuses on the balance of nonmaleficence and beneficence, according to which the clinical utility of benefit to the patient is measured against the risk of COVID19 exposure/infection. Solutions are provided by telemedicine and also clinical society guidelines of the ASTS, AASLD, and American Society of Transplantation.

Because most of these patients do not burden the critical resources needed by the COVID19 infection, the principle of justice is of low priority but not absent because the resources, like PPE and medical staffing, still need to be rationed and adjusted based on the burden of the pandemic in the local community.

## Conclusion

The SARS-CoV-2 pandemic has created a challenging environment both logistically and ethically for liver transplant programs. We anticipate that the evolving data on COVID19 in our patient population and improvement in testing and disease prevention will result in further management adaptations. While we continue to be faced with the issues of resource scarcity and challenged health care systems, we must use balanced ethical principles to help guide our approach to medical care and transplant practices. We must remain flexible and adapt to these unprecedented times while arming ourselves with the knowledge and skills to continue to deliver the best care to our patients.

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