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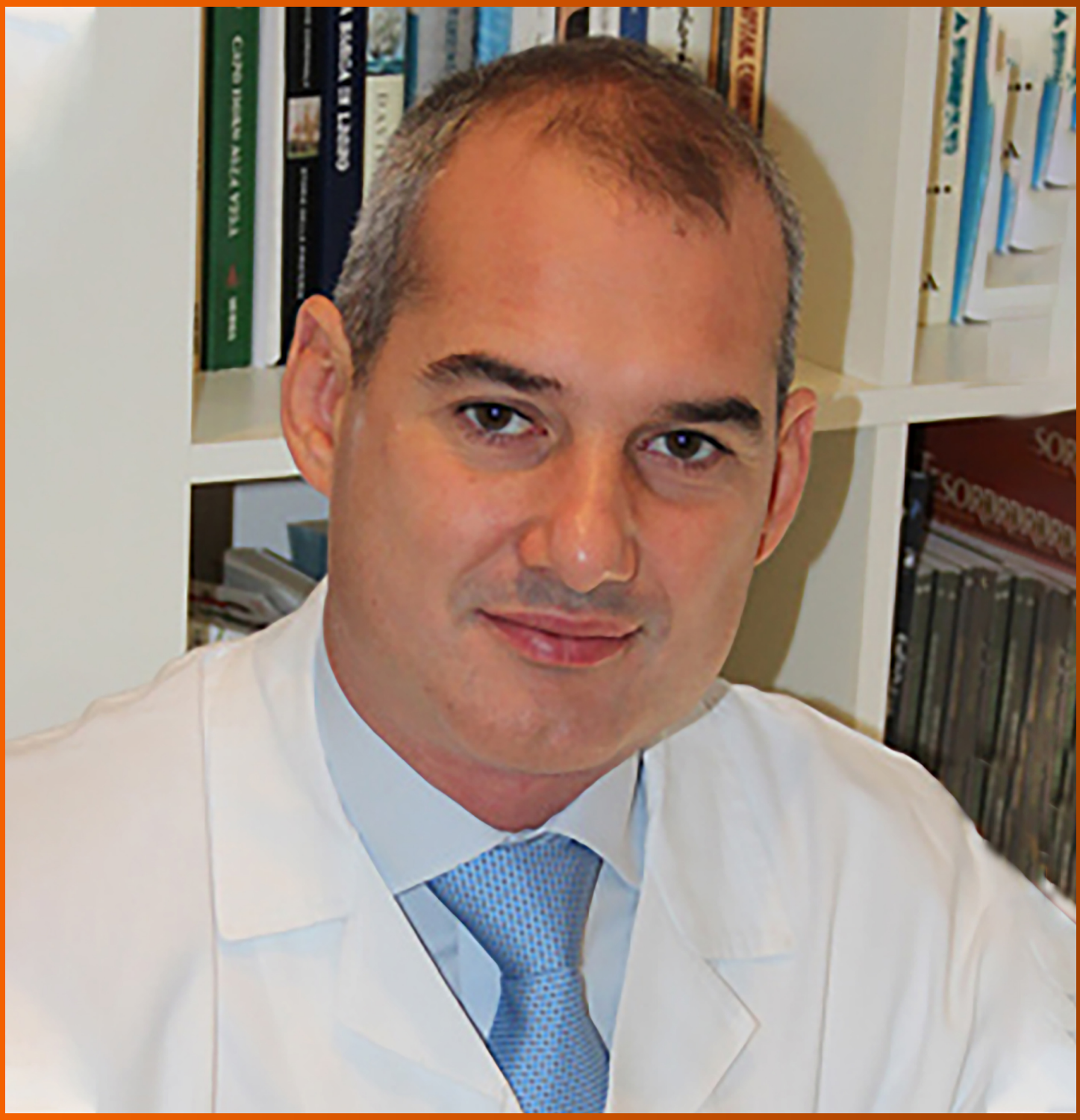

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REVIEW

Liver transplantation during global COVID-19 pandemic

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Abstract

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory disease respiratory syndrome coronavirus-2 has significantly impacted the health care systems globally. Liver transplantation (LT) has faced an unequivocal challenge during this unprecedented time. This targeted review aims to cover most of the clinical issues, challenges and concerns about LT during the COVID-19 pandemic and discuss the most updated literature on this rapidly emerging subject.

Key Words: COVID-19; Calcineurin inhibitors; Cytokine; Distributive justice; End-stage liver disease; Immunosuppression; Liver transplantation; Mortality

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Core Tip: This targeted review aims to cover most of the clinical issues, challenges and concerns about liver transplantation during the coronavirus disease 2019 pandemic and discuss the most updated literature on this rapidly emerging subject.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has significantly impacted the health care system globally. The virus is known to start in Wuhan, China, in 2019 and has now affected over 20 million people in the United States alone, with over 350000 deaths[1]. The causative agent severe acute respiratory disease respiratory syndrome coronavirus 2 (SARS-CoV-2) has a clinical range of clinical manifestations from asymptomatic infection to viral pneumonia, acute respiratory distress syndrome (ARDS), acute kidney injury, and immune hypersensitivity response leading to cytokine storm and vasodilated shock with multi-organ system failure and death[2-5].

Liver transplantation (LT) is the gold-standard treatment for end-stage liver disease (ESLD) patients. The cardinal challenge of any solid organ transplant is to successfully eliminate rejection of the transplanted organ graft with effective and tolerated immunosuppressive therapy. Induction therapy is initially started using anti-T-lymphocyte antibodies, which can be either polyclonal or monoclonal. Maintenance therapy commonly includes glucocorticoids, calcineurin inhibitors, and anti-proliferative agents. The goal of immunomodulating therapy is to keep a balance between minimizing the risk of rejection on the one hand and the risk of infections and malignancies on the other hand[6]. Being on immunosuppressive medications, it is unclear whether these drugs would reduce the risk of cytokine storm or result in more severe events during COVID-19 infection in these subjects.

CHALLENGES, FACTS, AND VIEWS

Liver transplantation is the only treatment option available for patients with acute fulminant hepatic failure, decompensated cirrhosis, or, under certain select circumstances, in hepatocellular malignancies[7]. The liver is the second most commonly transplanted organ after kidney transplants throughout the world[8]. Unlike in end-stage kidney disease, where renal dialysis can sustain life, there is no effective medical technology to replace liver function, rendering LT a truly lifesaving procedure. Although different viral infections have been associated with acute liver failure[9], apart from the component of multi-organ system failure, COVID-19 infection has so far only shown elevations in liver enzymes and mild elevation in bilirubin in critically ill patients[10].

Being a complex surgery requiring a lot of pre and post-procedural arrangements, monitoring and follow-up, LT has faced a significant stress burden when COVID-19 has emerged. One of the major arguments against the continuation of liver transplant procedures was the 20.5% mortality rate in patients who underwent elective surgeries during the incubation period of COVID-19 infection[11]. Adding to the challenge, being on immunosuppressive medications increases the subject's risk of worsening comorbidities and potentially lethal infection[12]. Nonetheless, case series have shown favorable clinical outcomes in COVID-19 patients on immunosuppressive medications, possibly because of the abated cytokine release syndrome[13,14]. Given the uncertainty of COVID-19 outcome in solid-organ recipients and the weighing risk-benefit of such a procedure, many transplant centers held all their transplant procedures at the beginning of the pandemic. Merola *et al*[15]. reported that the successful completion of liver transplant depends on multiple factors affected by the COVID-19 pandemic such as donor evaluations, organ recovery, organ procurement

organization availability, resources of donor hospitals, acceptance of organ offers by the transplant centers for their candidates. Moreover, the burden of the anticipated resource utilization needs to be considered at the performing transplant centers for carrying out the transplant procedures, such as the availability of ventilators, intensive care unit (ICU) beds, blood products and adequate staffing. In order to overcome these challenges, action plans were implemented. These included timely and reliable COVID-19 testing, limiting unnecessary travel, and promoting localized and central organ recoveries. The risk and resources for performing transplants at a particular center were closely assessed at all times in light of geographic constraints and local information regarding COVID-19 incidences in the hospital and the community at a given time[16].

As for deceased donor LT (DDLT), due to high mortality from COVID-19 infection, it has been questioned whether it was safe and appropriate to use the liver of patients who died of COVID-19 infection. There is a theoretical risk of infection to the recipients during DDLT and, in the absence of clear clinical consensus, it is left to the patients and individual transplant physicians to decide on this in the United States [17]. On the other hand, some countries already perform living donor LT (LDLT) due to deceased donor organ transplantation restrictions. This requires screening of the donors to decrease the risk of both transmission of COVID-19 infection and the risks to the donors themselves from the complications of the surgical procedures. It is recommended that living donors with confirmed active disease should wait until at least 28 days after the resolution of symptoms before transplantation[18].

Most recently he World Health Organization (WHO) and Center for Disease Control and Prevention (CDC) recommended a limitation in the outpatient and elective surgical procedures and use of personal protective equipment to limit the transmission during the first 2 waves of COVID-19 infection[7]. However, solid organ transplant is considered an essential urgent surgery; for example, the United States' Center for Medicare Services (CMS) designates it as a tier 3b procedure that should be continued when other elective surgical procedures are restricted[19]. To halt or continue with LT at the summit of the epidemic, challenges in DDLT and LDLT, many questions with unclear answers faced every transplant center worldwide.

EFFECT OF COVID-19 PANDEMIC ON LIVER TRANSPLANT ACTIVITIES

The disruption in the process of organ donation and recovery, especially in living donors, resulted in about a 25 % reduction in LT between March and May 2020 in the United States[15]. Taking a closer look at the situation, up until the beginning of May 2020, the rate of new listings or performance of DDLT in states with the lowest COVID-19 burden remained stable. On the other hand, in states with the highest incidence of COVID-19 infection, noticeably up to 34% fewer listings and DDLTs surgeries were observed. This could partially be attributed to lower hospital capacities accommodating an increased number of COVID-19 cases. Regarding Model for End-Stage Liver Disease (MELD) scores, there were 35.4% fewer DDLTs than expected for MELD 15-19 and 50.4% more DDLT than expected for MELD 30-34. Nonetheless, liver donor liver LDLT was 65% fewer than expected in states with the highest burden, likely due to its elective nature. In states with the highest COVID-19 incidence early in the pandemic, there was a 59% increase in waitlist mortality observed.

By August 2020, the overall volume transplant evaluations and listings were restored to pre-pandemic averages. While early in the pandemic, the COVID-affected areas had significant changes to their transplant practice, later in the pandemic, the new COVID-affected areas did not seem to be affected the same extent. Many reasons can explain this decline. The American Association for the Study of Liver Diseases (AASLD) Expert Panel and the CDC endorsed safety precautions and liberal use of telemedicine, enabling resumed functionality of the transplant centers. Moreover, elderly patients and those with comorbid conditions have avoided clinic and laboratory visits to minimize interaction and, hence, remove competing services in favor of resuming essential transplant evaluation and listing processes[20].

ETHICAL CONSIDERATIONS IN PATIENTS WITH COVID-19 AND LIVER TRANSPLANT

The rapid outbreak of COVID-19 led to a scarcity of resources and disrupted normal

operations in many hospitals and transplant centers worldwide[21]. During the six-month hiatus in performing LTs at a transplant center in Hong Kong, lower adherence to follow-up and two deaths were reported[22]. Similar situations have occurred in healthcare facilities across the world, which has prompted the urge to restructure the management of at-risk patients by use of ethical guidance to deliver appropriate health care[21]. Additional challenges imposed by the COVID-19 pandemic included, in addition to candidate prioritization and organ availability, distance in hard-to-reach location and issues with transportation to transplant centers, disproportionate disease burden in a given geographical area, all of which have led to the non-applicability of standard protocols[21]. These factors need to be taken into consideration during decision-making[21].

Beneficence, non-maleficence, justice, and autonomy are the fundamental ethical pillars that should guide decision-making to ensure that all patients are suitably considered for transplantation[21]. From an ethical perspective, there should be a balance between beneficence and non-maleficence when evaluating candidates, such that for a high-risk patient with a high MELD score, acute liver failure, or status 1A, beneficence is favored over minimized harm[21]. This is because an early liver transplant could confer the highest survival benefit in high-risk patients, although there is also the risk of exposure to SARS-CoV-2[21]. However, in low-risk patients, in whom transplantation is not imperative, exposure to SARS-CoV-2, on the other hand, could be more harmful[21]. Additionally, as per the principle of distributive justice, critical resources such as personal protective equipment (PPE) kits, hospital beds and health care worker manpower, *etc.*, should not be strained, directed, or diverged, especially during the COVID-19 pandemic[21].

A tiered approach to transplant surgery during the COVID-19 pandemic has been proposed, which shows the degree of reduction in transplantations that could be made based on the available resources, guided by ethical principles in decision making[23]. According to this tiered approach, transplant activity can be broken down from 0%, which is a state in which a health care system is wholly burdened and unable to provide surgeries, to 100% availability[23]. If in Tier 1 (0% capacity), given the complete lack of resources, consider transferring high-risk patients to alternative centers in case of an emergency[23]. In subsequent phases in which patients can be considered for transplantation, in phase 1 (Tier 2, 25% capacity), due to severe reduction in resources, surgeries should be prioritized for emergent cases only, *i.e.*, for immediately life-threatening conditions, *e.g.*, acute liver failure, MELD score > 30, or if the patient is unlikely to survive without intervention[23]. In phase 2 (Tier 3, 50% capacity), owing to a moderate reduction in resources, surgeries should be prioritized based on urgency; such as in those that are not immediately life-threatening or patients who cannot be managed in outpatient settings (acute liver failure or MELD score > 25), or for those who are unlikely to survive during the pandemic without intervention [23]. In phase 3 (Tier 4, 75% capacity), with a mild reduction in resources, elective cases should be considered, such as patients in non-life-threatening conditions, those who can be managed as outpatients with medical therapy, or if the patient is likely to remain stable for the duration of the pandemic[23].

With this guidance, the recommended stepwise evaluation can be helpful to assist healthcare centers to evaluate their capacity to deliver safe and effective surgical care and determine the level of surgical triage that can be accommodated[21]. The principle of distributive justice can be used to determine the best approach to allocate the available resources, especially to specific demographics, such as the elderly or lower socioeconomic groups[21].

INCIDENCE OF LIVER INJURY WITH COVID-19

In patients with COVID-19, the incidence of liver injury (defined by an alanine transaminase (ALT) and/or aspartate aminotransferase (AST) higher than threefold of the upper limit of normal, or gamma-glutamyl transferase (GGT) or total bilirubin higher than twofold of the upper limit of the normal reference range, is significantly higher in those with gastrointestinal symptoms, such as nausea, vomiting or diarrhea compared to those without gastrointestinal symptoms (17.57% *vs* 8.84%, $P = 0.035$)[24]. Chronic liver disease was found to increase ALT and AST levels, worsening liver injury from 14.8% to 53% in patients with COVID-19[25]. Liver injury was found to be more severe around the second week of the course of COVID-19 and is suspected to be related to SARS-CoV-2 infection of the regenerated liver cells from the bile duct, as indicated by high angiotensin-converting enzyme 2 (ACE2) expression in these cells[26].

Interestingly, the degree of liver injury was seen to vary with the severity of the symptoms of COVID-19[27]. In patients with severe symptoms of COVID-19, the incidence of liver injury was significantly higher than that in patients with mild symptoms (36.2% *vs* 9.6%, $P < 0.001$)[26,28-31]. It is strongly suspected that the liver injury was possibly an outcome following administration of multiple drugs off-label to treat COVID-19, such as lopinavir and ritonavir (18.6%)[30]. In another report, the liver function of patients with COVID-19 who were admitted to the ICU was significantly different from that of those out of the ICU[32]. According to two reports of the total COVID-19 related deaths, liver injury incidence was 58.06% and 78%, respectively[4, 33]. During statistical analysis of identifying risk factors leading to liver injury in patients with COVID-19, the occurrence of liver injury was seen to be only related to critical illness during multiple logistic regression, while patients who were administered several types of drugs were more likely to experience liver function injury ($P = 0.002$, $P = 0.031$, respectively)[26]. Thus, critical illness due to COVID-19 was established to be an independent risk factor for liver injury[26].

Surprisingly, the incidence of liver injury in patients with COVID-19 was also found to vary across geographical areas and age of patients[27]. One retrospective observational study reported that liver dysfunction was higher in the Wuhan province than in Jiangsu province[34]. This is possible because early detection and treatment of patients with COVID-19 in the Jiangsu province prevented liver injury, typically worsening as the SARS-CoV-2 infection increases in severity[27]. In reports on pediatric patients, thrombocytopenia accompanied by abnormal liver function was observed in two neonates born to mothers with COVID-19-related pneumonia[35]. In a single-center observational study, abnormal liver function was observed in four out of eight (50%) severe or critically ill pediatric patients with COVID-19[36].

MANIFESTATIONS AND OUTCOME OF COVID-19 IN LIVER TRANSPLANT PATIENTS

The typical presentation of COVID-19 includes cough, fever, myalgias, and headache. Indicators of more severe disease include dyspnea and oxygen requirement: less commonly diarrhea, sore throat, nausea, vomiting, and anosmia. Besides the usual symptoms described above, COVID-19 has been associated with rare cases of conjunctivitis, skin rash, venous and arterial thrombosis, encephalitis, Guillain-Barre syndrome, myocarditis, and pericarditis[37]. Concerning liver transplant recipients, clinical signs and symptoms have shown some slight variations. In some studies, clinical manifestations in liver transplant recipients have shown to have less incidence of fever, likely due to concomitant immunosuppressive therapy, while other studies have shown fever to be the most common finding. Other symptoms such as cough and dyspnea were reported to be similar in incidence as in the general population[38]. Diarrhea is another variation found to be more prevalent in solid organ transplant recipients than in the general population[38]. A literature review found that 90% of patients have fever as the most common symptom, followed by cough (36%), shortness of breath (31.8%), and diarrhea (31.8%)[39]. Another multi-center cohort study found that gastrointestinal symptoms such as diarrhea were more common in liver transplant patients than the general population, although respiratory symptoms seem similar[40]. The mechanism is thought to be due to the increased expression of ACE2 receptors in the intestine and liver[41].

A report of 12 cases of living donor liver transplants, 25% (3 patients) acquired SARS-COV-2 early within three months while 75% (9 patients) acquired it later within 18 mo post-transplant. The majority developed mild COVID19 disease except for 2 cases, one with acute renal injury and the other one had severe COVID19 complicated by cytokine storm and death. The latter was at 82 months post-transplant and suffered from multiple comorbidities (diabetes mellitus, hypertension, and chronic rejection) [42]. Another study that included 38 liver transplant recipients revealed that all those who died (7 patients) and 92% of those hospitalized had at least one comorbidity[43].

An international study including data of 151 adult liver transplant recipients and 627 consecutive non-transplant cases from 18 countries with confirmed SARS-CoV-2 infection who presented at the same period for medical care were compared to their outcome. The percentage of patients who needed hospitalization was similar in liver transplant and non-transplant groups (82% *vs* 76%, $P = 0.106$). Admission to ICU and the need for mechanical ventilation were significantly higher in the transplant group, 43 patients (28%) and 30 patients (20%) *compared to* 52 (8%) and 32 (5%) in the *non-transplant group* ($P < 0.0001$). Mortality, however, was lower in the transplant group

(19% *vs* 27%, $P = 0.0046$)[40]. A study in Spain that included 111 liver transplant recipients reported a lower mortality rate than the matched general population[44]. In another multi-center study, the strongest predictors of death were diabetes and acute liver injury, with 72.3% of included liver transplant recipients hospitalized, 26.8% required ICU-level care, and 22% expiring[45].

COVID-19 MORTALITY IN LIVER TRANSPLANT RECIPIENTS *VS* OTHER SOLID ORGAN TRANSPLANTS

According to a review by Alfishawy *et al*[46], based on studies published between January 1, 2020, and May 7, 2020, a total of 320 organ transplantations were reported; out of which 220 (69%) patients underwent kidney transplantation, 42 (13%) LT, 22 (7%) lung transplantation, 19 (6%) heart transplantation, 8 (3%) hematopoietic stem cell transplantation (HSCT), and 9 (3%) dual organ transplantation. Of the total number of patients who underwent organ transplantations, 69 (21.7%) patients were asymptomatic or mildly infected, 123 (38.7%) patients had a moderate infection, and 126 (39.6%) patients had severe infection[46]. However, the severity of COVID-19 infection in two organ transplant recipients in one study was not reported[46].

The overall mortality rate of the organ transplant recipients was 20% and all, except for two transplant recipients, had severe SARS-CoV-2 infection[46]. Comorbidities were observed in 38 cases (58% of total mortality), including hypertension in 58% of patients, diabetes mellitus in 29%, obesity or malignancy in 13%, ischemic heart disease in 11%, chronic obstructive pulmonary disease or hepatitis B in 5%, and bronchial asthma, hepatitis C virus disease, chronic kidney disease or HIV in 3%[46]. However, 14% of patients had no apparent comorbidities. In this cohort of recipients, ARDS was found to be the most frequent cause of death. Interestingly, hospital resource availability was not seen to affect the cause of death of organ transplant recipients[46]. All deceased transplant recipients had either reduced or stopped immunosuppressive therapy; however, no recipient had graft rejection, albeit no post-mortem exams were reported[46]. In this review, the deaths of 65 recipients were attributed to complications related to COVID-19[46].

In an American cohort of 90 patients, all adult solid organ transplant recipients from Columbia University Irving Medical Center and Weill Cornell Medicine, with a positive test for SARS-CoV-2 in an inpatient or outpatient setting were reviewed; of these, 46 (51%) patients were kidney recipients, 17 (18.8%) lung, 13 (14%) liver, 9 (10%) heart, and 5 (5.5%) dual-organ transplant recipients[38]. Sixteen organ transplant recipients were reported to die due to complications of COVID-19 [18% (16/90) overall, 24% (16/68) of all inpatients, 52% (12/23) of ICU patients][38]. Four of these patients who died preferred not to be admitted to the ICU or intubated. However, the age of these patients, clinical characteristics, or cause of death were not reported[38]. In another cohort of 18 solid organ transplant recipients with COVID-19 [8 (44%) kidney, 6 (33%) liver, and 3 (22%) heart] at a tertiary-care center in Madrid, the median age of transplant recipients was 71.0 ± 12.8 years, with median transplantation duration of 9.3 years and an overall case fatality rate of 28% was observed[47]. However, none of the patients discontinued immunosuppressive therapy[47].

In a case series of 5700 patients who were hospitalized with COVID-19 in the New York City area, 553 died; of these, those requiring mechanical ventilation ($n = 1151$, 20.2%), 282 (24.5%) died[48]. Interestingly, for male and female patients under 20 years, mortality was 0% (0/20); however, at every 10-year age interval over 20 years, mortality rates were higher for male than female patients[48]. Mortality rates were 76.4% and 97.2%, respectively, for patients who received mechanical ventilation in the 18-to-65 and older-than-65 age groups[48]. However, for those in the 18-to-65 and older-than-65 age groups who did not receive mechanical ventilation, the mortality rates were 1.98% and 26.6%, respectively[48]. Finally, a recent systematic review and meta-analysis of 2,772 solid organ transplant recipients [1500 (54.1%) kidney, 505 (18.2%) liver, 141 (5.1%) heart, and 97 (3.5%) lung] with SARS-CoV-2 infection reported overall mortality was 18.6%[49]. In terms of all-cause mortality, a pooled incidence of 22.0% was observed among kidney transplant recipients and 11.8% among liver transplant recipients[49]. In sum, mortality in patients with COVID-19 and organ transplantations was variable across different countries[46]. Mortality was higher in elderly transplant recipients with comorbidities[46]. Notably, there appears to be a higher incidence of mortality in solid organ transplant recipients than in the general population[49].

ADVICE FOR PREVENTION AND SURGICAL CONSIDERATIONS IN COVID-19 AND LIVER TRANSPLANT

As per the recommendations from the Beijing Working Party for LT, liver transplant recipients with fever or respiratory symptoms must promptly inform transplant centers and avoid unscheduled visits to avoid exposure[50]. Surgical considerations when operating on a liver transplant patient with COVID-19 include the use of PPE and extensive hand hygiene[7]. Also, limitations of aerosol-generating procedures like suction, endotracheal intubation, colorectal surgeries, colonoscopies, and advanced endoscopy to prevent disease transmission is recommended[7]. Before surgery, a detailed history of the patient should be taken along with repeated physical examination, temperature measurement, and chest imaging[7]. Non-emergency procedures should either be delayed or canceled[7].

Like the general population, recipients were instructed to stay home for safety, avoid in-person visits and public places, undergo frequent handwashing, advocate telework options, always use masks, call their transplant team if they get a fever or any respiratory symptoms, and arrange for a telemedicine visit if possible. Patients were instructed to avoid areas with high COVID-19 prevalence, and international travel was discouraged. Labs were only ordered if indicated and not just for routine follow-up; refills were supplied to avoid coming to the hospital. All patient education, waitlist status, social work, dietary and financial issues to be resolved *via* videoconferencing to avoid any gatherings and decrease psychological load[20].

Society guidelines and recommendations

Many society guidelines also were issued to address COVID-19 in transplant recipients. European Association for the Study of the Liver (EASL) and the European Society of Clinical Microbiology and Infection Diseases (ESMID) have issued a joint guideline for patients with liver disease. In the transplant section, they emphasized reducing direct exposure and more outpatient care while promoting telemedicine services with local laboratory testing and recommended against decreasing immune suppression[51]. Six months into the pandemic, another position paper was released and had more recommendations as screening donors with RT-PCR, close monitoring of drug levels, and recommended early admissions for COVID-19 transplant recipients [52].

American Association for the Study of Liver Diseases (AASLD) also have issued clinical guideline from an expert panel consensus during the pandemic had similar recommendations, but more detailed recommendations were added, including advice about staying home, ensuring availability of refills, and more inpatient care advice as to medication management and airway management[20].

Both EASL and AASLD recommended COVID-19 vaccines for patients with liver disease, but they were skeptical for liver transplant recipients given scarce data as the initial studies excluded transplant recipients, and there was a theoretical risk of immune-mediated rejection with newer vaccines[52,53].

MANAGEMENT OF LIVER TRANSPLANT RECIPIENTS WITH COVID-19

Immunosuppressed patients are among the risky groups susceptible to complications of COVID-19. On the other hand, protection from the inflammatory response responsible for tissue injury might be conferred due to immunosuppression[13]. According to clinical insights from AASLD, there is no need to reduce or stop immunosuppression for asymptomatic COVID-19 infected liver transplant recipients [54]. The WHO and the CDC strongly recommend that glucocorticoids (*i.e.*, dexamethasone, hydrocortisone, or prednisone) are to be given orally or intravenously for the treatment of patients with severe and critical COVID-19 based on evidence of mortality reduction of 8.7% and 6.7% in these cases[55,56] as well as avoiding adrenal insufficiency[57]. Decreasing the dose of immunosuppressive drugs should be only considered in the presence of critical illness or complications like drug-induced lymphopenia, bacterial or fungal superinfection in severe or rapidly progressive COVID-19. According to the patient's clinical status, antimetabolite drugs should be minimized or discontinued in the setting of worsening COVID-19 infection[58-60]. It is well known that early antiviral treatment ameliorates the course of the influenza virus; therefore, it can be assumed that early initiation of antiviral therapy may help to prevent COVID-19 pneumonia in high-risk groups[51]. In liver transplant recipients, caution should be taken to avoid bacterial or fungal superinfection or reactivation of

latent tuberculosis, HBV, and HSV[59].

Previous evidence from other viruses and SARS concluded that immunosuppression and comorbidities accompanied with solid organ transplantation might lead to severe clinical manifestations[61]. A study in Hong Kong included 29 Liver transplant recipients during the SARS outbreak in 2003, out of whom only four were treated for suspected SARS infection[22]. The authors concluded showed that immunosuppression in liver transplant recipients with COVID-19 may prolong the period of viral shedding but is not associated with increased mortality[22]. To date, there is no approved prophylactic drug against COVID-19 in liver transplant recipients[62]. The American Society of Transplantation recommends that all transplant patients and their households get vaccinated. In general, management of SARS-COV-2 infected transplant recipients should be a case-by-case approach, given that no specific treatment regimens are agreed upon till now. Essential considerations in managing COVID-19 in liver transplant recipients are drug-drug interactions and modifications of immunosuppression[51].

CURRENT IMMUNOSUPPRESSION REGIMEN AND IMPLICATIONS ON PHARMACOTHERAPY

Immunosuppressive medications used for transplant patients, such as tacrolimus, cyclosporine, and mycophenolate, are known to have relatively narrow therapeutic indexes and highly variable pharmacokinetic parameters[63,64]. Medication used for COVID-19 infection has numerous potential drug-drug interactions with immunosuppressive therapy utilized for transplant patients. Tacrolimus and cyclosporine are substrates of cytochrome P450 (CYP) 3A4 and the P-glycoprotein efflux pump. In addition, cyclosporine weakly inhibits CYP2C9, CYP3A4, and OATP1B1/1B3, as well as P-glycoprotein. Mycophenolate is a substrate of specific organic anion-transporting peptides (OATP) and UDP-glucuronosyltransferase enzymes. Drug-drug interactions are summarized in Table 1.

Antivirals

Remdesivir and favipiravir are novel adenosine analogs that inhibit SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), an essential enzyme required for viral replication[65,66]. *In vitro*, remdesivir is a substrate of CYP3A4, and the drug transporters OATP1B1 and P-glycoprotein and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and Multidrug and toxin extrusion protein 1 (MATE1)[67]. As of January 2021, remdesivir is the only FDA-approved antiviral therapy for COVID-19 patients requiring hospitalization and oxygen therapy[68]. Although no clinical interactions are expected between immunosuppressive agents and remdesivir, careful monitoring of drug concentrations and liver enzymes is recommended due to the lack of literature evaluating the concomitant use of these agents[64]. It should be discontinued if ALT surge ≥ 10x higher than the upper limit of normal[59]. Lopinavir/ritonavir are protease inhibitors of cytochrome P450 3A and was used for COVID-19 infection early in a pandemic. However, tacrolimus is metabolized by cytochrome P450 3A, and its serum level will be markedly elevated when PI is given. A kidney transplant recipient on tacrolimus and prednisone was reported to have serum tacrolimus level elevated because of drug-drug interaction when the patient was treated with lopinavir and ritonavir[49]. The level went back into normal therapeutic range a few days later after protease inhibitors were switched to favipiravir. Lopinavir/ritonavir should not be co-administered with sirolimus or everolimus, and close monitoring of immunosuppressive drug levels is mandatory[65]. Therefore, it is essential to monitor daily immunosuppressant (especially calcineurin inhibitors such as cyclosporin and tacrolimus) serum levels from transplant patients with COVID-19 and hold the immunosuppressant when drug-drug interaction is suspected.

Ivermectin

Ivermectin is an antiparasitic drug with an antiviral effect against SARS-COV-2 *in vitro*, with controversial efficacy in clinical trials[69]. Ivermectin has significant interactions with immunosuppressive drugs[60,65] further compromising off-label considerations.

Glucocorticoids

Glucocorticoids may play a critical role in managing profound systemic inflammation

Table 1 Interactions between commonly used severe acute respiratory disease respiratory syndrome coronavirus 2 antivirals and immunosuppressive drugs

	RDV	LPV/r	FAVI	HCQ	Ivermectin
Corticosteroids	None	Increase	None	None	None
Cyclosporine	None	Increase	None	Increase	None
Tacrolimus	None	Increase	None	Increase	Increase
Sirolimus	None	Increase	None	Increase	Increase
Mycophenolate	None	+/-	None	None	None
Azathioprine	None	None	None	None	None

Modified and adapted from El Kassas *et al*[7]. RDV: Remedisivir; LPV/r: Lopinavir/ritnovir; FAVI: Favipiravir; HCQ: Hydroxychloroquine.

associated with COVID-19 infection through the decreased production of inflammatory mediators and suppression of neutrophil migration[70]. Glucocorticoid preparations such as dexamethasone and methylprednisolone may decrease serum concentrations of tacrolimus through induction of CYP3A4 or CYP3A5[71]. This drug interaction may be more clinically significant regarding CYP3A5 as this interaction was not observed in patients who lacked CYP3A5 activity[71,72]. Additional monitoring of tacrolimus and sirolimus levels may be warranted when corticosteroids are initiated, tapered, or discontinued.

Tocilizumab

COVID-19 infection is thought to induce bronchial epithelial cell release of interleukin (IL)-6, a pleiotropic, pro-inflammatory cytokine produced by various cell types[73]. Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody approved for rheumatologic disorders and cytokine release syndrome[4]. *In vitro* studies in hepatocytes have shown that tocilizumab blocks IL-6-mediated downregulation of CYP450, mainly CYP3A4, and to a lesser extent CYP2C19[74]. Blocking downregulation of CYP450 would lead to increased CYP450 activity and decrease the bioavailability of medications metabolized through that pathway. However, its clinical significance is unclear as the downregulation of IL-6 activity was demonstrated in-vitro at very high concentrations[75]. Due to the long half-life elimination of approximately 13 days in adult patients, it is prudent to closely monitor transplant patients for a prolonged period after tocilizumab administration[76]. No sufficient data is available to recommend other immunomodulators like IL-1 inhibitors or interferon beta, while the role of tocilizumab for severe COVID 19 remains debatable[55].

Calcineurin inhibitors

Cyclosporine A and tacrolimus were found to inhibit the *in vitro* replication of various coronaviruses, including SARS-CoV at low concentrations[77,78]. Calcineurin inhibitors (CNIs) may also have a role in reducing COVID-19 induced cytokine storm. CNIs inhibit T-cell activation and suppress cytokines (IL-2, IL-4, TNF-α, and IFN-γ) that mediate the cytokine storm[79]. A multivariate analysis of 243 LT patients from 36 different facilities found that tacrolimus is associated with lower mortality of COVID 19 infection than other immunosuppressants such as cyclosporin mycophenolate mofetil and mTOR inhibitors[80]. A case of post-liver transplant patient on tacrolimus supported the point of no need for modification of immunosuppressant regimen when patients only present mild symptoms[81].

Anti-proliferative medication: Mycophenolate mofetil and mycophenolic acid

There is little evidence that mycophenolate mofetil (MMF) and mycophenolic acid (MPA) inhibit replication of coronaviruses *in vitro*[82-84], including SARS-CoV-2[85]. However, *in vivo* studies suggest that MPA may cause more harm than benefit in the case of Middle East Respiratory Syndrome- Coronavirus (MERS-CoV) infection[86, 87]. High doses of mycophenolate preparations were found to possibly increase the risk of severe COVID 19 in LT recipients. Withdrawal of mycophenolate mofetil or conversion to other immunosuppressants was suggested for COVID-19 infected LTRs in the same study[88]. Available data favor dose reduction or discontinuation of anti-proliferative medications in severe COVID-19 infection[89].

Mammalian target of rapamycin inhibitors

By inhibiting the effect of IL-37 and IL-38 in the inflammatory state, mammalian target of rapamycin (mTOR) inhibitors are considered to have a potential anti-COVID19 effect[90]. Also, the association between obesity and inferior outcome in COVID-19 patients has been previously described[91]. Targeting the mTOR pathway carries a potential for obesity treatment, thus theoretically can decrease the risk of severe COVID-19 infection[91,92].

Other adjunctive therapies

Various adjunctive therapies have been utilized to manage COVID-19, such as anticoagulation with heparin or vitamin supplementation with ascorbic acid, zinc, and thiamine. There are no known clinically significant drug interactions between immunosuppressive therapy for transplant patients and adjunctive treatment for COVID-19. Although with no proven benefit in COVID-19 patients yet still used in this cohort, chloroquine therapy may result in up to a 3-fold increase in cyclosporine A levels[93,94]. This interaction is not seen with tacrolimus[95]. Currently, insufficient data exist to recommend the use of convalescent plasma for COVID-19 patients except in clinical trials[60]. It appears to be valid only if given early in the course of the disease and containing a high titer of immunoglobulins[55].

PEDIATRIC LIVER TRANSPLANT

Compared to adults, the pediatric population has a milder disease and rarely requires hospitalization. Data from the largest pediatric LT center in Lombardy, Italy, have shown little affection for pediatric liver transplant patients and suggested that immune suppression might be protective and recommended continuing transplant programs [96]. A survey was conducted for healthcare professionals across the European reference network on pediatric transplantation (ERN-TransplantChild) showed 12/18 transplant centers reducing usual activity with modification of outpatient visits and incorporating telemedicine tools. Reported cases in the survey did not show any severe cases in pediatric liver transplant recipients[97]. An another survey of the European Liver and Intestine Transplantation Association (ELITA) and European Liver Transplant Registry (ELTR) showed that during the height of the pandemic, 1% of liver transplant centers selected only children and 1% selected only high urgency children[98].

An Iranian pediatric study that included 40 newly transplanted liver recipients during the height of the pandemic there showed no affected children by COVID-19 and had the same conclusion as prior studies promoting continuing regular transplant programs[99]. A multi-center United States study has shown similar results with all pediatric transplant recipients showing mild to moderate presentation (including 10 Liver transplant recipients), and this study concluded that COVID-19 in such population may mirror those of immunocompetent children[100]. A Japanese group had another finding in 20 pediatric liver transplant procedures in the COVID-19 era with increased incidence of intraoperative portal vein thrombosis, although it was not statistically significant[101]. In India, similar results were reported, with one center reported no COVID-19 development in their cohort of 7 recipients during the pandemic, and this was attributed to strict protocol adopted by the hospital there[102].

CONCLUSION

In sum, mortality in patients with COVID-19 and LTs was variable across different countries. Mortality was higher in elderly transplant recipients with comorbidities. Notably, there appears to be a higher incidence of mortality in solid organ transplant recipients than in the general population. Immunosuppressive drugs in this cohort should be carefully tailored on a case-by-case basis.

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