



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Review article

Liver transplantation in the era of COVID-19

Mohamed El Kassas^{a,*}, Mohamed Alborai^b, Amira Al Balakosy^c, Nermeen Abdeen^d,
Shimaa Afify^e, Mohammad Abdalgaber^f, Ahmed F. Sherief^c, Ahmad Madkour^a,
Mohamed Abdellah Ahmed^b, Mohamed Eltabbakh^c, Mohamed Salaheldin^c,
Mohamed-Naguib Wifi^g

^a Endemic Medicine Department, Faculty of Medicine, Helwan University, Cairo, Egypt

^b Department of Internal Medicine, Al-Azhar University, Cairo, Egypt

^c Tropical Medicine Department, Ain Shams University, Cairo, Egypt

^d Tropical Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt

^e Gastroenterology Department, National Hepatology And Tropical Medicine Research Institute, Cairo, Egypt

^f Gastroenterology and Hepatology Department, Police Authority Hospitals, Giza, Egypt

^g Internal Medicine Department, Hepatogastroenterology Unit, Kasr Al-Ainy School Of Medicine, Cairo University, Cairo, Egypt



ARTICLE INFO

Article history:

Received 21 April 2020

Accepted 29 April 2020

Keywords:

COVID-19

Coronavirus

Liver transplantation

ABSTRACT

Liver transplantation is considered the ultimate solution for patients with end-stage chronic liver disease or acute liver failure. Patients with liver transplant need special care starting from preoperative preparation, surgical intervention ending with postoperative care. Transplanted patients have to receive immunosuppressive therapy to prevent rejection. Such a state of immune suppression could predispose to different types of infections in liver transplant recipients. Currently, the world is suffering a pandemic caused by a new strain of the coronavirus family called COVID-19. Certain infection control precautions are needed to protect immunocompromised and vulnerable patients, including liver transplant candidates and recipients from acquiring COVID-19 infection. Restricting non-transplant elective surgical procedures, managing transplant patients in separate outpatient clinics, and in-patient wards can prevent transmission of infection both to patients and healthcare workers. Telemedicine can help in the triage of patients to screen for symptoms of COVID-19 before their regular appointment. Management of immunosuppressive therapy and drug-drug interactions in liver transplant recipients infected with COVID-19 should be cautiously practiced to prevent rejection and effectively treat the underlying infection. In this report, we are trying to summarize available evidence about different aspects of the management of liver transplant candidates and recipients in the era of COVID-19.

© 2020 Pan-Arab Association of Gastroenterology. Published by Elsevier B.V. All rights reserved.

Contents

Introduction	70
COVID-19 and liver transplantation	70
Surgical considerations during operating COVID-19 patient	70
Indications of liver transplantations in COVID-19 era	70
Donor risks and care during COVID-19 pandemic	71
Precautions for preparation of patients before liver transplantation	71
Post-operative care for liver transplant patients during COVID-19 era	71
ICU care for liver transplantation in the era dominated by COVID-19	72
Possible drug-drug interactions between liver transplantation medications and COVID-19 therapy	72
Chloroquine and hydroxychloroquine	73
Remdesivir	73

* Corresponding author at: Endemic Medicine Department, Faculty of Medicine, Helwan University, Cairo, Egypt.

E-mail address: m_alkassas@hq.helwan.edu.eg (M. El Kassas).

Favipiravir	73
The lopinavir-ritonavir combination	73
Tocilizumab	73
Ribavirin	73
Interferon beta	73
Management of liver transplant patients on immune suppressive therapy to prevent the acquisition of COVID-19	73
References	74

Introduction

The 2019–20 coronavirus outbreak is an ongoing pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The outbreak was identified in Wuhan, China, in December 2019, declared to be a Public Health Emergency of International Concern on 30 January 2020, and recognized as a pandemic on 11 March 2020 [2,3]. As of 16 April 2020, more than 2 million cases of COVID-19 have been reported in 213 countries and territories [1]. Liver transplantation (LTX) is the second most common solid organ transplantation worldwide after kidney transplantation. The overall global LTX rate is 3.7 per million population [4,5]. Indications of LTX also vary according to geography. In developed countries, HCV has been the main indication for LTX, although it is now being replaced by alcoholic liver disease, non-alcoholic liver disease (NAFLD), and hepatocellular carcinoma (HCC), while in Asia; hepatitis B and HCC remain a common indication for LTX [6,7]. In Arab countries, 3,804 liver transplants were performed in the period 1990–2013 in which Living donor liver transplantation (LDLT) represented 80%, and deceased donor liver transplantation (DDLT) represented 20%. Fifty-six percent of the reported cases were in Egypt [8].

COVID-19 and liver transplantation:

Based on previous observations for SARS and other related viruses, a theoretical risk of liver damage exists with COVID-19 infection [9,10]. However, available data only reported hepatic dysfunction in the form of abnormal levels of liver aminotransferases and slightly elevated bilirubin levels, mainly in critically ill patients [11]. On the other hand, reports during an influenza outbreak in Germany in winter 2017/2018 showed increased organ failure scores of patients with liver cirrhosis where 5 out of 11 patients with liver cirrhosis developed acute liver failure during influenza infection [12]. No data available on the impact of COVID-19 on decompensated liver disease patients awaiting LTX, but because of the known immunocompromised state of these patients, adequate protective measures should be maintained. Although healthcare facilities are overwhelmed with management of COVID-19 patients & health resources are being rapidly consumed, the American Association for the Study of Liver Diseases (AASLD), recommended against postponing transplantation. Moreover, they advised each program to consider its capability regarding intensive care unit (ICU) beds, ventilators availability, and blood donation [10]. Prioritization of transplant candidates is another problem that may face clinicians due to limited resources during the pandemic, as well as the exclusion of donors infected with COVID-19 [10]. Immunosuppression in the post-transplant recipients may be protective against cytokine storm induced by COVID-19, which is responsible for the severe illness on the one hand. However, and on the other hand, recipients on immunosuppression may have more intense and prolonged shedding of the virus, increasing the risk of transmission to contacts, including healthcare workers [13]. This could emphasize the crucial role of implementing infection control measures to avoid losing candi-

dates on the LTX waiting list because of the closed transplantation centers [14].

Surgical considerations during operating COVID-19 patient:

International societies like World Health Organization (WHO) and Centre for Disease Control and Prevention (CDC) are always confirming the necessity to use Personal Protection Equipment (PPE) in addition to the restriction of outpatient and elective procedures as preventive measures against COVID-19 [15]. Limitations of aerosol-generating procedures like suction, endotracheal intubation, and advanced endoscopy are of major concern due to the fear of the possibility of disease transmission. Further restrictions to prevent other routes of infections like feco-oral transmission, included colorectal surgeries and colonoscopies. Currently, many interventional surgical societies, anesthesia, endoscopy, radiology, and intensive care have placed their statements, guidelines, and recommendations to adjust their practice to the current epidemic [16]. Different reasons rationalized the delay or even cancellation of non-emergency procedures as they would consume PPE tools which are currently running short supply worldwide. The second reason that such elective procedures are postponed or canceled is to prevent unnecessary infections to medical staff and caregivers, which may be transmitted from asymptomatic COVID-19 patients or their companions. Also, they consider such procedures a further burden and workload on an already exhausted medical system. Finally, occupying the operative theatres with such cases would warrant the need for mechanical ventilators that might be more beneficial and valuable if they are directed to rescue a COVID-19 patient's life [17]. Meticulous evaluation should be done before deciding for the priority of the procedure through detailed history taking, one by one consultation, temperature measurement, hand hygiene, and reporting of any suspected case of COVID-19 (even if afebrile), and finally cleaning and disinfection protocols of premises. Repeated physical examination and temperature measurement along with the revision of chest imaging like a computed tomography scan or a chest radiograph, and if COVID-19 is suspected or confirmed, all non-emergency procedures would be delayed or canceled [18].

Indications of liver transplantations in COVID-19 era

Because of the rapidly changing situation of COVID-19 infection worldwide, indications of LTX will need to be updated according to the emerging data. Bearing in mind that any liver transplant related activity not only involves the donor and the recipient, but it involves many individuals, including doctors, paramedical staff, nurses, and health care workers. Taking into consideration that there is a risk of the donor to recipient transmission of COVID-19, from both deceased donors and living donors. The risk of donor-derived infection would depend upon donor exposure, infectivity in the incubation period, degree and duration of viremia, and viability of the virus within blood or specific organ compartments [13]. Traditionally, The AASLD/AST guidelines outline four major types of indications for LTX in the United States: Acute liver failure, complicated cirrhosis, metabolic liver diseases, and sys-

temic complications of chronic liver disease [19]. Acute liver failure is the most important indication for emergency LTX. Common causes of acute liver failure include acetaminophen overdose, acute viral hepatitis, drug-induced liver injury, mushroom poisoning, autoimmune hepatitis, Wilson's disease, acute ischemic hepatitis (shock liver), and acute fatty liver of pregnancy [19–22]. Similarly, patients with cirrhosis and type 1 hepatorenal syndrome have a median survival of fewer than two weeks and should be urgently referred to a transplant center for expedited transplant evaluation, as should patients with other evidence for rapid hepatic decompensation [19,23].

Elective LTX is indicated in cases with cirrhosis associated with deteriorating hepatic synthetic function, renal function, and related complications like HCC [19,24–31]. To minimize the risk of COVID-19 exposure in the hospital setting, LTX should be done judiciously as per the following criteria. In essence, non-urgent transplants should be postponed, and acute liver failure can be done according to the standard indications, acute on chronic Liver failure decisions for transplantation should be based on individual center's experience [32].

Donor risks and care during COVID-19 pandemic

Despite being potentially transmitted by organ donation, recent recommendations suggest that LTX could be performed during the COVID-19 pandemic [10]. As the organism is predominantly found in respiratory secretions, lungs are considered high-risk organs for transmission of COVID-19 infection if the donor is infected. However, all other organs could be considered at risk as the virus was isolated from blood in nearly 15% of cases [33]. These observations are supported by evidence from the SARS epidemic in 2003 in which autopsy results could demonstrate the virus in almost all body organs [34].

Two types of LTX techniques are available; the first is the conventional or standard method, which involves implantation of whole liver grafts DDLT, and this type is the most widely used in the USA and Europe [19]. The other type is LDLT, and this is the only option available for patients living in some countries like Egypt as cadaveric organ transplant is still banned there, and that is why some patients travel abroad seeking organ transplant elsewhere [35]. At present, the organ procurement organizations (OPOs) and hospitals having LDLT programs should screen potential donors for exposure and clinical symptoms suggestive of COVID-19, and as more information builds up, the ideal approach would hopefully be developed [36]. Although personal contact is the basis of the doctor-patient relationship, which allows rapid and accurate assessment of the patient's condition, unfortunately, it exposes physicians to the risk of infection and becomes a source of the virus spread. Therefore, it is considered wise to substitute direct contact with patients with more distant interactions with the utilization of available technology. The same approach could also be applied to the post-operative period for the donor in the case of LDLT, aiming to be discharged as soon as possible from the hospital [37]. With the increasing number of infected cases and mortality caused by COVID-19, a recent discussion for using organs from patients infected with COVID-19 has led to several points of debate. For instance, from the clinical point of view, it could potentially be a life-saving procedure, especially that delays might result in more deterioration for the patient's need for the organ and even increase the risk of COVID-19 exposure. On the other hand, it may transmit infection, which would even be more severe in transplant recipients, especially in the absence of effective therapy. Financially speaking, it can be a possible source of income for hospitals despite reimbursements remain uncertain. It might be argued from the legal point that organs with HCV have

already been transplanted after getting informed consent from patients. Nevertheless, this disease has a different risk profile compared to HCV. As regards the ethical perspective, this procedure respects the wishes of donors and their families and ensures the autonomy of patients willing to do so. However, patients could be overwhelmed with responsibility for informed consent in the presence of little guidance [38].

Precautions for preparation of patients before liver transplantation

The emergence of the COVID-19 pandemic has posed extensive threats and problems to all the healthcare facilities, including LTX centers [39]. These effects are not only confined to donor or recipient issues but also extends to involve many other problems in the availability of healthcare resources [13]. We are faced with enormous challenges owing to the high communicability and virulence of the virus, the risk of introducing immunosuppressive therapies during this pandemic, and our utmost need for all the health care utilities. On the other hand, we do have a very long list of miserable patients waiting for LTX, which is the only available treatment option for this difficult to treat a group of patients, so judicious decisions and strict precautions became now mandatory [40]. Streptococcal pneumonia and influenza vaccines are strongly recommended to all recipients prior to LTX, together with strict prophylaxis against complications of cirrhosis to reduce the number of hospital admissions [41]. It is also recommended to test for COVID-19 in patients with acute decompensation or Acute on top of chronic liver failure (ACLF) [39]. For those on LTX lists, it is recommended to test both donors and recipients for COVID-19 before LTX, putting into consideration that negative results do not totally exclude the infection. Alternatively, computed tomography (CT) of the chest can be considered [42]. Pre-procedure consent should include the potential hazard for the acquisition of nosocomial COVID-19 infection [39]. Accepting only grafts with a low risk of delayed graft function to reduce complications and minimize the length of postoperative stay is also recommended [10]. Diminishing exposure of health care workers as much as possible, through using online clinics and phone calls as a substitute to primary clinics can prevent unnecessary risk of infection. Doctors may also talk to all patients by phone before their visits to rule out any possibility of COVID-19 infection. Deferring optional visits and restricting it only to urgent ones also help to prevent nosocomial infections [37]. Modifications of the outpatient transplant clinics by widening the patients' waiting areas and following strict infection control precautions is of utmost importance [43].

Workforce affairs are crucial; any member of the transplantation team suffering from any symptom suggestive of COVID-19 infection should be absent from work and self-isolate him/herself for fourteen days if the exposure occurred. Moreover, a rapid test for the transplantation team is highly recommended [44].

Post-operative care for liver transplant patients during COVID-19 era

Post-operative care for LTX recipients during the pandemic of COVID-19 is challenging. To guarantee the maximum benefits for both the patient and the graft, a multidisciplinary management team is usually involved in postoperative care of LTX recipients. Such management includes infection control with extra care directed at preventing postoperative infections, including COVID-19 infection [40].

Liver transplant recipients should be admitted to separate wards where there is complete separation from COVID-19 admission wards, along with the strict implementation of standard disin-

fection measures. It is recommended to limit surgical and medical rounds, requests for the image, and blood tests to the least required number [10]. Follow up of Liver transplant recipients is usually performed in tertiary referral hospitals, where COVID-19 hotspots may be present [39]. It is thus recommended to limit in-person outpatient visits even in areas without significant COVID-19 community spread [45]. Hospital admission of liver transplant recipients should be considered only for patients suffering from major complications like rejection, decompensation, or vascular complications. During in-person outpatient follow up visits, liver transplant recipients should be evaluating in dedicated hepatology/liver transplant clinics away from clinics where confirmed or suspected cases of COVID-19 are evaluated [10]. Once the patient is clinically stable, it is recommended to perform his routine laboratory investigations, including drug levels at primary care facilities [39]. Telemedicine can mitigate exposure of both patients and healthcare workers to COVID-19 as it allows better physician-patient communication. Development of COVID-19 symptoms (fever, cough, shortness of breath, sore throat, diarrhea, the new loss of sense of taste or smell, contact with known COVID-19 patients, history of recent travel) in a liver transplant recipient should prompt urgent referral for evaluation along with hepatic symptomatology surveillance and drug compliance assurance [37,46].

ICU care for liver transplantation in the era dominated by COVID-19

Epidemics can lead to a significant increase in demand for ICU beds, so reducing the available beds. As an example, the SARS outbreak in Toronto led to closures of 35 ICU beds for ten days, which represented 38% of the tertiary-care university medical-surgical beds of ICU in Toronto [47]. Many reasons represent a challenge in caring for patients with COVID-19 with a high risk of exposure for ICU staff. COVID-19 is highly contagious, along with more than one route of transmission. The high exposure dose, long contact hours with cases, some procedures such as noninvasive ventilation, and the length of ICU stay are representing the challenges for ICU staff during the epidemic [48]. So, special measures and precautions should be taken in intensive care. For example, cases with COVID-19 should be admitted to single bedded and negative pressure rooms in separate units within intensive care. Clinical engi-

neering should have rapid and special plans to convert standard rooms into ICU rooms. Retrofitting the rooms with externally exhausted HEPA filters may solve the problem [49]. Most of the transplanted patients have multiple comorbidities and organ dysfunction, demanding high appropriate critical care management to support prompt graft recovery and prevent systemic complications [50]. The early postoperative period is a critical time. Strict monitoring of vital data, support of cardiorespiratory performance, early assessment of graft function, along with recognition of unexpected complications (medical and surgical) are mandatory. The Intensive care management of liver transplanted patients mainly focuses on rapid hemodynamic stabilization, early weaning from mechanical ventilation, coagulopathy correction, preservation of kidney function, graft rejection prevention, proper fluid administration, and infection prophylaxis [50].

Based on the current situation with the conflict of the limited capacity of ICU beds and the urgent need for transplantation in some cases, safety protocols should be applied in transplant centers with experience exchange between them. A recent protocol applied in one of the major centers of LTX in Portugal is to test new liver transplant cases with PCR for COVID-19 and arrange for transfer other medical or surgical critically-ill patients to the nearest other ICUs inside the hospital or outside, to ensure the ICU beds availability for new liver transplant cases. Moreover, patients and staff from each sector of the ICU should use different routes inside the ICU to decrease the risk of infection [51]. Another way to minimize the possibility of ICU admissions is by applying the fast track protocols which can be applied safely for selected patients undergoing either living or DDLT [52]. The definition of fast-tracking in liver transplant still lacks consensus among different centers, ranging from early postoperative extubating in the operating room once the surgery is finished, to strategies that minimize postoperative ventilation time. Generally, this term is reserved for early extubation, recovery in a post-anesthesia care unit (PACU), and direct transfer to the surgical ward avoiding an ICU stay [53,54].

Possible drug-drug interactions between liver transplantation medications and COVID-19 therapy

Patients who underwent LTX are usually poly medicated using many drug classes. The most important are immunosuppressive

Table 1
Possible drug-drug interactions between SARS-CoV-2 antiviral drugs and commonly used immunosuppressants for liver transplant recipients.

	ATV	LPV/r ♥	RDV	FAVI	CLQ ♥	HCLQ ♥	RBV	TCZ	IFN-β
Hydrocortisone	↑	↑	↔	↔	↔	↔	↔	↔	↔
Prednisone	↑	↑	↔	↔	↔	↔	↔	↔	↔
Prednisolone	↑	↑	↔	↔	↔	↔	↔	↔	↔
Methylprednisolone	↑	↑	↔	↔	↔	↔	↔	↔	↔
Cyclosporine	↑	↑	↔	↔	↑	↑	↔	↓	↔
Tacrolimus	↑	↑ ♥	↔	↔	↑ ♥	↑ ♥	↔	↓	↔
Sirolimus	↑	↑ ♥	↔	↔	↑	↑	↔	↓	↔
Mycophenolate	↔	↑↓	↔	↔	↔	↔	↔	↔	↔
Azathioprine	↔	↔	↔	↔	↔	↔	↑	↔	↔
Anti-thymocyte globulin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Basiliximab	↔	↔	↔	↔	↔	↔	↔	↔	↔

Abbreviations:

ATV: Atazanavir, LPV/r: Lopinavir/ritonavir, RDV: Remdesivir, FAVI: Favipiravir, CLQ: Chloroquine, HCLQ: Hydroxychloroquine, RBV: Ribavirin, TCZ: Tocilizumab, IFN-β: Interferon beta.

♥: These drugs have been identified as having a known or possible QT or TdP risk.

↑ Potential increased exposure of the comedication.

↓ Potential decreased exposure of the comedication.

↔ No significant effect

Boxed color code:

Black: These drugs should not be coadministered.

Dark grey: Potential interaction which may require a dose adjustment or close monitoring.

Light grey: Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required.

White: No clinically significant interaction expected.

drugs. As most anti-COVID-19 agents are investigational, drug-drug interactions are very critical in this situation in those fragile patients. Possible drug-drug interactions between SARS-CoV-2 antiviral drugs and commonly used immunosuppressants for liver transplant recipients are presented in [table 1](#) [55–57]. Possible interactions with other drugs are summarized below:

Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine act either as viral entry blockers or as immunomodulators. Despite encouraging preliminary reports, side effects, and interactions with other medications are well known [55]. Chloroquine has potential interactions with commonly used drugs like ampicillin, amlodipine, azithromycin, propranolol, and antacids [56]. Chloroquine has significant drug interaction with ciclosporin as it increases levels of cyclosporin by decreasing its metabolism. Also, Chloroquine increases levels of tacrolimus by the same mechanism but to a lesser extent [56].

Remdesivir

Remdesivir is a nucleotide analog with broad-spectrum antiviral activity against single-stranded RNA viruses [55]. It is an investigational drug that appears safe and may not affect other medications; however, Remdesivir concentration can be affected by enzyme inducers like Clarithromycin, Rifampin, Phenytoin, and Phenobarbital [57].

Favipiravir

It is also an investigational drug with antiviral activities through its selective inhibition of viral RNA-dependent RNA polymerase [55]. Favipiravir increase concentration of pioglitazone, rosiglitazone, paracetamol, oseltamivir, and hormonal replacement therapy; however, no significant interactions with immunosuppressive medications nor steroid [57].

The lopinavir-ritonavir combination

A fixed-dose combination for the prevention and treatment of HIV infection. The cytochrome P450 inhibitory effects of ritonavir prolong the half-life of Lopinavir and extend its protease inhibitory action but, on the other hand, increases its liability for many drug interactions [55]. This combination is not recommended to be co-administer with many steroids forms, simvastatin, atorvastatin, domperidone, and sirolimus. There is also a potential interaction with ciclosporin, mycophenolate, tacrolimus, which makes its use in the setting of LTX is questionable. However, a recent case report confirmed successful COVID-19 treatment by Lopinavir/ritonavir in liver transplant recipients [58]. Lopinavir/ritonavir can increase chloroquine and hydroxychloroquine concentrations. Also, Lopinavir/ritonavir induces QT interval prolongation that may potentiate chloroquine and hydroxychloroquine toxicity [57].

Tocilizumab

Tocilizumab is a monoclonal antibody that targets the interleukin-6 receptor, which is the possible mediators of COVID-19 induced inflammation and cytokine storms [55]. It has potential possibly minor interaction with ciclosporin, tacrolimus, and sirolimus. Tocilizumab can reduce concentrations of calcineurin inhibitors with necessary drug level monitoring. Its use with chloroquine and hydroxychloroquine may have additive toxicity. Also, It may potentiate hematological toxicity of ribavirin and interferon-beta if used together as Tocilizumab has a myelosuppressive effect [57].

Ribavirin

Ribavirin is an old antiviral drug used in the treatment of HCV for years, and that had a role in the treatment of SARS. As it causes dose-dependent hemolytic anemia, Ribavirin may potentiate the hematological toxicity of Interferon-beta and Tocilizumab. Ribavirin had no significant interaction with immunosuppressive drugs [57].

Interferon beta

One of the lessons learned from MERS-CoV infections is that host inflammatory responses play a major role in disease progression. This was the base of using interferon-beta in MERS-CoV and COVID-19 infections [55]. In the setting of LTX, Interferon-beta had no interactions with immunosuppressive drugs or steroids. Nevertheless, it induces myelosuppression, so it should not be combined with Tocilizumab. Also, potential interaction with chloroquine and hydroxychloroquine may increase its toxicity [57].

Management of liver transplant patients on immune suppressive therapy to prevent the acquisition of COVID-19

Patients with advanced liver disease and those after LTX represent vulnerable patient cohorts with an increased risk of infection and/or a severe course of COVID-19. Because of the immunosuppressed state they have [59]. As the innate immune response associated with increased serum interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF- α) levels may be the main driver for pulmonary injury due to COVID-19, immunosuppression may be protective [33,60]. Coronaviruses have not shown to cause more severe disease in immunosuppressed patients. More interestingly, reviewing the mortality and morbidity reports published on Coronaviruses outbreaks such SARS that emerged in 2002, MERS, and more recently COVID-19, no fatalities were reported in patients undergoing transplantations, receiving chemotherapies or other immunosuppressive treatments [61]. Risk factors for poor outcome include older age (post-transplant recipients aged greater than 60 years old) male sex and presence of comorbidities (obesity, diabetes, heart disease, lung disease, kidney disease) [10]. Available data on coronavirus before and during outbreaks suggest that immunosuppressed patients are not at increased risk of severe pulmonary disease compared to the general population; however, immunosuppression may prolong viral shedding in post-transplant patients with COVID-19 if they are already infected [36,60]. Immunosuppressive therapy should be started in patients with liver disease with or without COVID-19 who have strong indications for treatment (e.g., autoimmune hepatitis, liver transplant patients, and in cases of graft rejection). This should be done without compromising their transplant management as reducing the dosage or stopping immunosuppressants as this may precipitate acute rejection in a liver transplant recipient, so there is no need to reduce or stop immunosuppression for asymptomatic post-transplant patients without known COVID-19 [10]. The reduction should only be considered under special circumstances (e.g., medication-induced lymphopenia, or bacterial/fungal superinfection in case of severe COVID-19) after consultation of a specialist [62]. The potential role of corticosteroids for the prevention of progression of mild COVID-19 to severe pneumonia is unknown. WHO recommends avoiding corticosteroids for the treatment of COVID-19 unless indicated for another therapeutic purpose [63]. In patients with confirmed COVID-19, we should minimize the dosage of prednisone, maintaining a sufficient dosage to avoid adrenal insufficiency [39]. Similarly, it is also advised to reduce

daily calcineurin inhibitor dosage; consider decreasing tacrolimus/cyclosporine by 50%, stop mycophenolate (CellCept/Myfortic) and Azathioprine especially in the setting of lymphopenia, fever, or worsening pneumonia attributed to COVID-19. In the case of ground-glass opacities, pneumonia switching mammalian target of rapamycin (mTOR) to calcineurin inhibitors (CNI, e.g., tacrolimus) should be done given the possibility of pneumonitis with mTor; otherwise, we should stop all immunosuppression [59]. For outpatients on belatacept, switching to tacrolimus or cyclosporine should be considered after 28 days from the last dose, to avoid clinic visit. For inpatients on belatacept, we should not administer any further belatacept. Twenty-eight days after the last dose, adding low dose CNI should be considered. For CNI intolerant patients, increasing daily prednisone dose from 5 mg to 7.5–10 mg daily might be considered. Low dose prednisone (5 mg) in all patients who were receiving it before hospitalization can be maintained [59].

References

- World Health Organization. "Coronavirus disease 2019". <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. Accessed April 14, 2020.
- World Health Organization. Novel Coronavirus – China. <https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>. Accessed April 13, 2020.
- World Health Organization. Director-General's opening remarks at the media briefing on COVID-19—11 March 2020". <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020>. Accessed April 13, 2020.
- Carmona M, Álvarez M, Marco J, et al. Global organ transplant activities in 2015. data from the global observatory on donation and transplantation (GODT). *Transplantation* 2017;101.
- Organ donation and transplantation activities, 2015 report. www.transplant-observatory.org/organ-donation-transplantationactivities-2015-report-2. Accessed April 12, 2020.
- Trotter JF, Cardenas A. Liver transplantation around the world. *Liver Transpl* 2016;22:1059–61.
- Chen CL, Kabiling CS, Concejero AM. Why does living donor liver transplantation flourish in Asia?. *Nat Rev Gastroenterol Hepatol* 2013;10:746–51.
- Amer and Marwan. Living donor liver transplantation in Egypt. *HepatoBiliary Surg Nutr* 2016;5(2):98–106.
- Hui DS, Azhar IE, Madani TA, Notumi R, Kock O, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020;91:264–6.
- AASLD. Clinical Insights for Hepatology & Liver Transplant providers during the COVID-19 Pandemic. <https://www.aasld.org/sites/default/files/2020-04/AASLD-COVID19-ClinicalInsights-4.07.2020-Final.pdf>. Accessed April 13, 2020.
- Zhang B, Zhou X, Qiu Y et al. Clinical characteristics of 82 death cases with COVID-19. <https://www.medrxiv.org/content/10.1101/2020.02.26.20028191v1> accessed on April 13, 2020.
- Schütte A, Ciesek S, Wedemeyer H, et al. Influenza virus infection as precipitating event of acute-on-chronic liver failure. *J Hepatol* 2019;70:797–9.
- Michaels MG, La Hoz RM, Danziger-Isakov L, Blumberg EA, Kumar D, Green M, et al. Coronavirus disease 2019: Implications of emerging infections for transplantation. *Am J Transplant* 2020. <https://doi.org/10.1111/ajt.15832>.
- AlGhamdi M, Mushtaq F, Awn N, Shalhoub S. MERS CoV infection in two renal transplant recipients: case report. *Am J Transplant* 2015;15:1101–4.
- World Health Organization: Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19). Interim guidance. Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/infection-prevention-and-control>. Accessed April 12, 2020.
- El Kassas M, Al Shafie A, Abdel Hameed AS, Mahdi M. Emergency endoscopic variceal band ligation in a COVID-19 patient presented with hematemesis while on mechanical ventilation. *Dig Endosc* 2020. <https://doi.org/10.1111/den.13694>.
- American College of Surgeons ACS: COVID-19: Elective Case Triage Guidelines for Surgical Care. <https://www.facs.org/covid-19/clinical-guidance/elective-case>. Online March 24, 2020. Accessed April 12, 2020.
- Chen Xiangdong, Liu Yanhong, Gong Yahong, Guo Xiangyang, Zuo Mingzhang, Li Jun, et al. Chinese Society of Anesthesiology, Chinese Association of Anesthesiologists; Perioperative Management of patients infected with the novel coronavirus: recommendation from the joint task force of the Chinese Society of Anesthesiology and the Chinese Association of Anesthesiologists. *Anesthesiology* 2020. <https://doi.org/10.1097/ALN.0000000000003301>.
- Martin P, DiMartini A, Feng S, Brown Jr R, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014;59:1144–65.
- Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases position paper on acute liver failure 2011. *Hepatology* 2012;55:965–7. <https://doi.org/10.1002/hep.25551>.
- Lee WM. Acute liver failure. *Semin Respir Crit Care Med* 2012;33:36–45.
- Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137:947–54.
- O'Leary JG, Lepe R, Davis GL. Indications for liver transplantation. *Gastroenterology* 2008;134:1764–76.
- Yu L, Ioannou GN. Survival of liver transplant recipients with hemochromatosis in the United States. *Gastroenterology* 2007;133:489–95.
- Silverman EK, Sandhaus RA. Clinical practice. Alpha1-antitrypsin deficiency. *N Engl J Med* 2009;360:2749–57.
- Ahmad A, Torrazza-Perez E, Schilsky ML. Liver transplantation for Wilson disease. *Handb Clin Neurol* 2017;142:193–204.
- Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. *N Engl J Med* 2017;377:2063–72.
- Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011;141:1249–53.
- Iqbal S, Smith KA, Khungar V. Hepatopulmonary syndrome and portopulmonary hypertension: implications for liver transplantation. *Clin Chest Med* 2017;38:785–95.
- Cosarderioglu C, Cosar AM, Gurakar M, et al. Portopulmonary hypertension and liver transplant: recent review of the literature. *Exp Clin Transplant* 2016;14:113–20.
- Porres-Aguilar M, Zuckerman MJ, Figueroa-Casas JB, Krowka MJ. Portopulmonary hypertension: state of the art. *Ann Hepatol* 2008;7:321–30.
- Saigal S, Gupta S, Sudhindran S, et al. Liver transplantation and COVID-19 (Coronavirus) infection: guidelines of the liver transplant Society of India (LTSI). *Hepatol Int* 2020. <https://doi.org/10.1007/s12072-020-10041-1>.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)* 2020;395(10223):497–506.
- Kumar D, Humar A. Emerging viral infections in transplant recipients. *Curr Opin Infect Diseases* 2005;18(4):337–434.
- El-Meteini M, Fayed A, Fathy M, et al. Living related liver transplantation in Egypt: an emerging program. *Transpl Proc* 2003;35(7):2783–6.
- American Society of Transplantation. 2019-nCoV (Coronavirus): FAQs for organ donation and transplantation. Published March 20, 2020. <https://www.myast.org/sites/default/files/COVID19%20FAQ%20Tx%20Centers%2003.20.20-FINAL.pdf>. Accessed April 2020.
- Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. *N Engl J Med* 2020.
- American society of Transplantation. COVID-19 Organ Donation and Transplantation Town Hall (Donor Issues and Candidate Concerns) [Online]; American society of Transplantation 2020 12–4-2020. Podcast. Available from: <https://www.youtube.com/watch?reload=9&v=0xaFpTba0T8t&> accessed April 13, 2020
- Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020. <https://doi.org/10.1016/j.jhepr.2020.100113>.
- Kumar D, Manuel O, Natori Y, Egawa H, Grossi P, Han S-H, Fernandez-Ruiz M, Humar A. COVID-19: A global transplant perspective on successfully navigating a pandemic. *Am J Transplant* 2020. <https://doi.org/10.1111/ajt.15876>.
- Fagiuoli S, Colli A, Bruno R, et al. Management of infections pre- and post-liver transplantation: Report of an AISF consensus conference. *J Hepatol* 2014;60(5):1075–89.
- Winichakoon P, Chaiwarith R, Liwsrisakun C, et al. Negative nasopharyngeal and oropharyngeal swab does not rule out COVID-19. *J Clin Microbiol* 2020. <https://doi.org/10.1128/JCM.00297-20>.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA* 2020 [Internet] available from : <https://jamanetwork.com/journals/jama/fullarticle/2762130external> accessed on April 13, 2020.
- World Health Organization. Coronavirus disease (COVID-19) outbreak: rights, roles and responsibilities of health workers, including key considerations for occupational safety and health; available from: https://www.who.int/docs/default-source/coronaviruse/who-rights-roles-respon-hw-covid-19.pdf?sfvrsn=bcabd401_0 accessed on April 13, 2020.
- CDC. Cleaning and Disinfection for Community Facilities. <https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/cleaning-disinfection.html> accessed on April 13, 2020.
- Terry K. Telehealth seen as a key tool to help fight COVID-19. *The Hospitalist*. Published March 6, 2020. <https://www.the-hospitalist.org/hospitalist/article/218574/coronavirus-updates/telehealth-seen-key-tool-help-fight-covid-19>. Accessed April 2020.
- Dwosh HA, Hong HH, Austgarden D, Herman S, Schabas R. Identification and containment of an outbreak of SARS in a community hospital. *CMAJ* 2003;168(11):1415–20.
- Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382(13):1199–207. <https://doi.org/10.1056/NEJMoa2001316>.
- Al-Dorzi HM, Aldawood AS, Khan R, et al. The critical care response to a hospital outbreak of Middle East respiratory syndrome coronavirus (MERS-

- CoV) infection: an observational study. *Ann Intensive Care* 2016;6(1):101. <https://doi.org/10.1186/s13613-016-0203-z>.
- [50] Feltracco P, Barbieri S, Galligioni H, Michieletto E, Carollo C, Ori C. Intensive care management of liver transplanted patients. *World J Hepatol* 2011;3(3):61–71. <https://doi.org/10.4254/wjh.v3.i3.61>.
- [51] Cardoso FS. Liver transplantation in an ICU dominated by COVID-19. *Liver Transpl* 2020.
- [52] Taner CB, Willingham DL, Bulatao IG, et al. Is a mandatory intensive care unit stay needed after liver transplantation? Feasibility of fast-tracking to the surgical ward after liver transplantation. *Liver Transpl* 2012;18:361–9.
- [53] Mandell MS, Stoner TJ, Barnett R, et al. A multicenter evaluation of safety of early extubation in liver transplant recipients. *Liver Transpl* 2007;13:1557–63.
- [54] Glanemann M, Busch T, Neuhaus P, et al. Fast tracking in liver transplantation. Immediate postoperative tracheal extubation: feasibility and clinical impact. *Swiss Med Wkly* 2007;137:187–91.
- [55] Gasmí A, Noor S, Tippairote T, Dadar M, Menzel A, Bjørklund G. Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic [published online ahead of print, 2020 Apr 7]. *Clin Immunol* 2020;108409. <https://doi.org/10.1016/j.clim.2020.108409>.
- [56] Drug interaction checker. <https://reference.medscape.com/drug/aralen-chloroquine-phosphate-chloroquine-342687#3> accessed April 13, 2020
- [57] COVID-19 Drug Interactions. <https://www.covid19-druginteractions.org> accessed April 13, 2020.
- [58] Bin L, Yangzhong W, Yuanyuan Z, Huibo S, Fanjun Z, Zhishui C. Successful Treatment of Severe COVID-19 Pneumonia in a Liver Transplant Recipient [published online ahead of print, 2020 Apr 3]. *Am J Transplant* 2020. <https://doi.org/10.1111/ajt.15901>.
- [59] Massachusetts General Hospital COVID-19 Treatment Guidance. <https://www.massgeneral.org/news/coronavirus/treatment-guidance> accessed April, 13, 2020.
- [60] D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic [published online ahead of print, 2020 Mar 20]. *Liver Transpl*. 2020;10.1002/lt.25756. doi:10.1002/lt.25756.
- [61] Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. *Lancet Infect Dis* 2018;18(8):e217–27. [https://doi.org/10.1016/S1473-3099\(18\)30127-0](https://doi.org/10.1016/S1473-3099(18)30127-0).
- [62] Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression [published online ahead of print, 2020 Mar 17]. *Am J Transplant* 2020. <https://doi.org/10.1111/ajt.15869>.
- [63] World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected) Accessed online April 13, 2020.