

COVID-19 pandemic: Its impact on liver disease and liver transplantation

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Abstract

Severe pulmonary disease caused by the novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)], has devastated many countries around the world. It has overwhelmed the medical system. The priorities of many institutions have changed to manage critically ill corona virus infectious disease-2019 (COVID-19) patients, which affected the working style of many departments. Hepatologists and transplant surgeons look after a very sensitive patient group. Patients with liver disease need special attention and continuous follow-up. Similarly, transplant candidates also need special care. Healthcare professionals in the field of hepatology face the overwhelming task of taking care of COVID-19 patients with hepatic complications, liver disease or transplant patients who are SARS-CoV-2 positive, and the patients on routine surveillance who do not have COVID-19. This review will evaluate COVID-19 from the perspective of its effect on the liver and its possible effects on patients with liver disease. Furthermore, the level of care for liver transplant recipients during the pandemic will be discussed.

Key words: SARS-Cov-2; COVID-19; Acute liver injury; Chronic liver disease; Liver transplantation; Risk factors

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Core tip: Data regarding the effect of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on liver transplant (LT) recipients are very limited. We have performed 35 living donor liver transplantations since the first corona virus infectious disease-2019 (COVID-19) case was observed in Turkey. We routinely test living liver donors and recipients for SARS-CoV-2 with nasopharyngeal swabs before the liver transplantation procedure. Furthermore, we repeated this test before discharging the patients. We have not found any SARS-CoV-2-positive LT recipients or donors, nor have we found any patients with COVID-19-like pneumonia. We have limited the number of patients going to the outpatient clinic, and only performed LT when it was urgently needed. We took the necessary precautions to protect the healthcare personnel

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by limiting the duration of work and providing protective equipment to all, including inpatients.

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INTRODUCTION

A new strain of coronavirus that caused severe respiratory disease in infected individuals was initially identified in China's Wuhan City in December 2019^[1]. The International Committee on Taxonomy of Viruses named the new virus: Severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2), which was responsible for the corona virus infectious disease-2019 (COVID-19)^[2]. It soon spread to almost every country around in the world, and the World Health Organization declared that COVID-19 was a Public Health Emergency of International Concern on January 30, 2020. To date, there are 5061476 confirmed cases and 311475 deaths globally^[1]. In Turkey, the first case was declared on March 11, 2020, and as this review article was written, there are 154500 confirmed cases and 4276 deaths due to COVID-19 (total test: 1767495)^[3].

The mortality rate of the disease is thought to be 2%-5% in the general population. However, patients who were older, or had underlying diseases, such as hypertension, diabetes, and chronic obstructive pulmonary disease, are considered high-risk with a mortality rate of > 50%^[4]. To date, there is no definitive treatment for COVID-19. However, agents such as remdesivir are effective in decreasing the duration to recovery and the incidence of the respiratory disease and seems promising^[5]. Although respiratory symptoms dominate the clinical picture in COVID-19, it is unclear whether the virus causes infections in multiple organs. The present study aimed to evaluate the pathophysiology of COVID-19 and to analyze the implications of this disease for medical centers that facilitate and manage liver transplantation and acute and chronic liver disease.

PATHOGENESIS OF SARS-COV-2 INFECTION

SARS-CoV-2 is a new virus belonging to the beta coronavirus genus^[6], and is a positive-strand RNA virus that has a glycolipid envelope^[7]. The virus recognizes the angiotensin-converting enzyme 2 (ACE-2) receptor to infect host cells^[8]. This section will attempt to delineate the viral entry and replication process. ACE-2 is present in cardiomyocytes and most endothelial cells except for those lining the liver sinusoids, lungs, bile ducts, intestines, and kidneys^[9]. Through the infection of these tissues, the virus can be isolated from blood, feces, urine, and secretions of the upper and lower respiratory tract. Although the main route of entry into the body is through inhalation of respiratory microparticles, the oral-fecal route cannot be dismissed because viral RNA has been found in fecal samples^[10].

The spike protein (S protein) is a ligand on the SARS-CoV-2 surface that binds to ACE-2. Potential targets for this protein include ACE-2 and C-type lectin (L-SIGN or CD209L)^[11]. After attaching to the cell membrane, the virus is internalized when the viral envelope fuses with the host membrane^[12]. The viral genome enters the cytoplasm and is translated to form new virions. There are two open reading frames (ORFs) in the viral genome (ORF1 and ORF2)^[13]. Translation of ORF1 yields structural and nonstructural proteins, which facilitates viral genome replication^[14,15].

Once the structural proteins are formed, massive copies of the viral genome are synthesized. The structural proteins are incorporated into the membrane of the endoplasmic reticulum (ER) and Golgi complex^[14]. Once the viral genome is replicated, it interacts with and becomes attached to the structural proteins and this complex enters the lumen of the ER-Golgi intermediary compartment (ERGIC) to form a nucleocapsid^[16]. Once this process is completed, mature virions are transported to the cell membrane inside ERGIC vesicles and released into the extracellular space upon vesicles-membrane fusion^[16].

THE INTERACTION OF SARS-COV-2 AND THE IMMUNE SYSTEM

The role of the major histocompatibility antigens

The viral nucleocapsid proteins remain on the surface of the cell membrane after the virus has entered the cell *via* fusion with the host membrane; these are recognized by antigen-presenting cells, which initiate an antiviral immune response^[7]. The common antigen presenting cells in humans are dendritic cells, monocytes, plasma cells, *etc.* Viral antigens are presented to cytotoxic (CD8+) and regulatory (CD4+) T lymphocytes by the major histocompatibility complexes, which are also called human leukocyte antigens (HLAs). In particular, HLA class I antigens play an important role during this process^[17].

We know very little about SARS-CoV-2 and the antigens involved in the immune response to this virus. However, our experience with the 2003 SARS pandemic has provided important information regarding the role of HLA class I and II antigens. From the SARS pandemic, we know that certain HLA class I and II alleles, such as HLA IB4601, IB07033, and IIDRB1-1202^[18,19], increase an individual's susceptibility to coronavirus. In contrast, the HLA II DR0301, Cw1502, and IA 0201 alleles confer resistance to SARS and Middle-East respiratory syndrome (MERS) infections^[20].

Interaction of SARS-CoV-2 with components of the host immune system

Our current SARS-CoV-2 knowledge is based on our experiences from previous pandemics (SARS and MERS). Unfortunately, the host-viral interactions for SARS-CoV-2 have not been clearly defined. However, we can follow its immunopathogenesis based on our observations of patient symptoms^[21,22]. People become infected when they breathe in the respiratory secretions (droplets and microdroplets) from infected individuals come into contact with their respiratory tract. The median interval between the exposure to the development of the symptoms is 6 d (range: 2-14 d)^[2,11,23]. The main features in infected patients were lymphopenia and elevated serum levels of pro-inflammatory cytokines^[11,23,24]. Chronologically, these phenotypes coincide with the appearance of bilateral "ground glass" opacities in the lungs^[21]. Lin and colleagues hypothesized that the viral cycle has three phases: (1) Viral entry and viremia; (2) Pneumonia; and (3) Recovery phase^[21]. The first two phases occur in all patients when SARS-CoV-2 somehow evades the immune system. If the immune system is strong and the virus is cleared away, the patient recovers. However, if the immune system is dysfunctional, such as in individuals with hypertension, cardiovascular disease, or diabetes, there will be a late inflammatory response that results in a cytokine storm. In this scenario, the patient's condition deteriorates to a critical level^[21,25]. In the present section, we summarize the interactions between the virus and the components of the innate and adaptive immune system.

The main mechanism for viral immune evasion begins at the innate immune response level. Viral defense against the host immune system involves: (1) Infection of a limited number of cells over a large surface area; and (2) Blockage of the main host immune defense, such as the interferon (IFN) type I response and its downstream pathways^[25]. As we have stated earlier, the main receptor for SARS-CoV-2 cellular entry is ACE-2, and the main entry route to the body is *via* inhalation of microdroplets into the lower respiratory tract. The ACE-2-positive alveolar cells comprise only a fraction of the cells of the respiratory tract^[9,26]. Therefore, only a limited number of cells across a large surface area are initially infected, which may "dilute" the initial viral load. As a result, density of infected cells are initially low and virus replicating and disseminating without evoking a major response in the host immune system. The IFN type I pathway plays a key role in the initial defense against viral infection. Pathogen-associated molecular patterns, which constitute the viral RNA and the intermediate double-stranded RNAs that are formed during viral replication, are recognized by certain receptors on the ER, which initiates an internal signal for the IFN type I response. Downstream of this pathway, the Janus kinases and signal transducer and activator of transcription proteins are phosphorylated and activated, and the IFN-stimulated genes are transcribed. The IFN related genes are comprised of vast number of chemokines and cytokines that stimulate both the innate and the adoptive immune system. All these result in apoptosis of the infected cells and immune cell recruitment^[16]. Both SARS and MERS coronaviruses block the IFN type I response by either dephosphorylating or ubiquitinating the intracellular receptors and effectors in this pathway^[27]. SARS-CoV-2 could also inhibit this pathway *via* the same mechanism because it is genomically similar to the SARS (80%) and MERS (nearly 50%) viruses^[28]. Furthermore, our experiences with SARS and MERS showed us that coronaviruses could infect local macrophages and T cells^[29]. The innate immune system plays an important role in the clearance of the virus. If the innate immune

system is successful in clearance of the virus in the early stages then the infection resolves without any problem. However, if the viral clearance is unsuccessful, the late IFN type I response results in the release of a variety of proinflammatory cytokines are synthesized and released which results in a hyperinflammatory state which is called the cytokine storm. Therefore, the efficiency of the function of the innate immune system determines the prognosis of the^[7,25]. In individuals with an intact innate immune system, the virus is cleared during the initial phase, and this is the reason why children and healthy young adults who contract the disease have mild symptoms. However, the elderly and individuals with underlying chronic diseases have an altered innate immune response and the viral clearance is not sufficient leading to cytokine storm and which has devastating effects^[24].

In certain patient groups with poorer prognostic outcomes, the discharge of cascade of pro-inflammatory cytokines (cytokine storm syndrome) results in a hyper-inflammatory state, which exacerbates pulmonary dysfunction and may lead to multi-organ failure^[29]. Cardinal feature of the cytokine storm syndrome resemble hemophagocytic lymphocytosis. Both entities manifest as persistent fever, cytopenia, and hyperferritinemia. Pulmonary dysfunction is also a prominent feature of this disease, affecting more than 50% of patients^[30]. Huang and colleagues^[24] showed that the levels of pro-inflammatory cytokines, such as interleukin (IL)-2, IL-7, granulocyte colony-stimulating factor (GM-CSF), IFN- γ inducible protein (IP)-1, monocyte chemoattractant protein (MCP), macrophage inflammatory protein (MIP)-1 α , and tumor necrosis factor (TNF)- α are increased in COVID-19 patients. Yang *et al.*^[31] analyzed 53 COVID-19 cases (34 severe versus 19 moderate). They showed that patients with moderate disease were generally younger (63.2% were between 16-59 years of age in moderate cases; 73.5% of severe cases were over 60 years old). Both pro- and anti-inflammatory cytokines were elevated in the COVID-19 cases. In particular, IP-10, MCP-3, and IL-1ra levels predicted the disease severity and mortality of patients because these cytokines were persistently elevated in a majority of severe cases (for up to 15 d from admission) and 14 fatal cases^[31]. Therefore, cytokine storm syndrome is a potential target for developing new therapeutic modalities to treat critical cases and to reduce mortality. Monteleone *et al.*^[32] published an editorial proposing that patients should be treated with anti-IL-6 therapy, normally used to treat hyperactive immune diseases, such as rheumatoid arthritis, as it may protect patients from the pulmonary complications observed in COVID-19 patients. This may be due to the fact that IL-6 lies at the center of the cytokine cascade involved in cytokine storm syndrome.

The type 1 T helper response to viral infections is extremely important because it provides a memory response against the virus. It is important to orchestrate humoral and cytotoxic T cell responses during viral infections^[25,33]. This adaptive immune response targets certain viral antigens, such as the S, N, M, and E proteins. While there are insufficient data on the adaptive immune response to SARS-CoV-2; our experience from SARS patients tells us that the immunoglobulin (Ig)M response begins 9 d post-infection, and continues for 12 wk^[25,34]. In the second week following viral entry, IgG response kicks in. The IgG response can be observed for up to two years after the initial viral infection^[34]. The number of peripheral blood CD4+ and CD8+ lymphocytes is reduced in COVID-19 patients and we do not know the implications of this observation^[7,35]. However, during the SARS pandemic, the CD4+ T cell activity is overwhelmed by the CD8+ T cell response. Furthermore, a type 2 T helper response was observed in patients with severe disease, and elevation of IL-4, IL-5, and IL-10 cytokines was the dominant immune response in critically ill patients^[36]. In addition, early cytotoxic T cell responses predicted disease severity and mortality in patients^[37]. Cumulatively, these results suggest that we should focus on promoting the type 1 T helper responses and preventing excessive cytotoxic T cell responses in patients when developing treatment and vaccination for COVID-19.

ACUTE LIVER INJURY IN PATIENTS WITH COVID-19

The SARS-CoV-2 S protein is expressed in tissues during the viral replication cycle and causes inflammation in most tissues, including the liver. This inflammatory response facilitates viral clearance from the tissues and promotes an adaptive immune response to viral infection^[38]. CD4+ lymphocytes promote the transformation of B cells into plasma cells and enhance antibody production. Cytotoxic T lymphocytes are active in most tissues, which reflects an effective antiviral response, but may also cause extensive tissue injury. Therefore, as previously mentioned, events that lead to a hyper-inflammatory state cause tissue immunopathogenesis, which may result in tissue injury during COVID-19^[39]. However, the exact mechanisms by which an

extrapulmonary organ, such as the liver, is affected by SARS-CoV-2 infection is not known. In this section, we will summarize the current cases and outline the liver-related pathologies in these patients.

One of the points of discussion for this subject is whether viral liver injury occurred as a direct or indirect consequence of COVID-19^[38]. ACE-2 is expressed by cholangiocytes but not by Kupffer cells, hepatocytes, or sinusoidal endothelial cells^[9,40]. In animal models, ACE-2 expression was elevated after partial hepatectomy, which was maintained until the end of the regenerative process^[41]. This elevated expression was attributed to an increase in cholangiocyte activity, including its own proliferation and differentiation to hepatocyte differentiation^[38,42]. Therefore, ACE-2 is a surrogate marker for hepatic regeneration. We hypothesized that in living donor liver transplantation (LDLT), the ACE-2 protein is also upregulated in the tissue and serum. Therefore, during the early postoperative phase, both the liver transplant (LT) recipients and donor tissues are more susceptible to SARS-CoV-2 infection because they have an elevated ACE-2 protein expression as a consequence of hepatic regeneration.

Gamma-glutamyltransferase and alkaline phosphatase are known surrogate markers of cholangiocyte and bile duct damage^[38]. Patient data accumulated since the beginning of the pandemic in Wuhan, China, have shown that the level of aminotransferase had increased, whereas, that of cholestatic enzymes had not (Table 1)^[4,24,42-50]. Approximately 20% of cases in descriptive and phase IV clinical trials of new therapeutic approaches had elevated aminotransferase^[48]. Furthermore, the duration and severity of this disease affected aminotransferases levels, which peaked at around the second and third week following the onset of symptoms^[44,49]. This observation suggests that the mechanistic basis of tissue injury may not be directly related to the viral infection.

The liver is a highly intricate filtration machine that detoxifies portal blood of the xenobiotics that originate from the intestines. This liver function can be disrupted by extreme physiological stress. Cytokine storm is one of the most potent physiological stresses that result in a hyper-inflammatory condition and leads to organ damage^[51,52]. High levels of IL-2, IL-6, IL-7, IL-10, TNF- α , GM-CSF, IP-10, MCP-1, and MIP-1 α were observed in patients with severe COVID-19^[51,52]. Furthermore, acute liver injury was more prominent in these patients^[47]. For this reason, there must be a correlation between acute liver injury and cytokine storm, both of which were observed in the severe form of COVID-19.

Sepsis is a common clinical condition in COVID-19 patients and is also a major physiological stress^[38,53]. Many mechanisms can cause end-organ damage during sepsis. Reactive oxygen species, ischemia-reperfusion injury, sepsis-induced cholestasis, and drug toxicity injury are some of the mechanisms that could cause sepsis-induced liver injury. Furthermore, hypo-perfusion and a hyper-inflammatory state result in an unfavorable microenvironment that leads to liver injury^[54,55]. The main COVID-19 liver damages are moderate microvesicular steatosis and mild inflammation at the lobules and portal region, which reflects drug toxicity^[35,56]. COVID-19 patients consume certain drugs, such as paracetamol, oseltamivir, abidol, and lopinavir/ritonavir, which are known to be hepatotoxic^[57,58]. Therefore, a combination of virus-mediated hyper-inflammatory state and drug hepatotoxic result in the acute liver injury observed in COVID-19 patients. However, the effects of SARS-CoV-2 infection on patients with underlying liver diseases, such as hepatitis B virus (HBV) and hepatitis C virus infections, non-alcoholic steatohepatitis, and ethanol toxicity, are not known. The following sections will evaluate the effect of SARS-CoV-2 in patients with chronic liver disease and those who have undergone liver transplantation.

COVID-19 IN PATIENTS WITH UNDERLYING LIVER DISEASE

Although evidence is lacking, patients with chronic liver diseases may be more susceptible to SARS-CoV-2 infection. Biologic drugs used to treat COVID-19, such as tocilizumab and baricitinib, can result in the reactivation of diseases, such as HBV infections^[56]. There are two points to be considered. The first is SARS-CoV-2's effect on patients with underlying liver disease, and the second is how this virus changes the standard of care for patients with liver disease.

While we do not have enough clinical evidence to properly dissect the first point, an early postmortem study has shown that the virus was found in the liver tissue of a patient who had died from COVID-19^[59]. In the same study, one patient had cirrhosis, but the liver histopathologic examination result was inconclusive. However, three

Table 1 The summary of the clinical studies about acute liver injury in coronavirus infectious disease-2019

Ref.	Total patients	No. of ALI, n (%)	No. of severe disease among ALI, n (%)	Number of dismal prognosis among ALI, n (%)
Zhou <i>et al</i> ^[41]	191	59 (38.8)	NS	26 (44.1)
Huang <i>et al</i> ^[24]	41	15 (36.6)	8 (53.3)	NS
Guan <i>et al</i> ^[41]	1099	326 (29.7)	94 (28.8)	46 (14.1)
Hu <i>et al</i> ^[43]	323	265 (82)	134 (50.6)	58 (21.9)
Zhang <i>et al</i> ^[45]	115	28 (24.3)	20 (71.4)	NS
Yang <i>et al</i> ^[44]	149	45 (30.2)	NS	NS
Fu <i>et al</i> ^[46]	350	101 (28.8)	NS	14 (13.9)
Cai <i>et al</i> ^[47]	298	44 (14.7)	21 (47.7)	NS
Cao <i>et al</i> ^{[48]1}	199	120 (60.3)	NS	NS
Shi <i>et al</i> ^[49]	81	43 (53.1)	26 (83.7)	NS
Omrani-Nava <i>et al</i> ^[50]	93	27 (29.2)	NS	NS

It was considered acute liver injury if the patients had elevated alanine aminotransferase, aspartate aminotransferase, or both or if acute liver injury is reported by the authors.

¹All were severe cases. ALI: Acute liver injury; No.: Number of individuals dismal prognosis; progression of the disease despite suitable therapy of occurrence of mortality in the patients; NS: Not specified.

other patients who did not have a history of liver disease exhibited signs of hepatic damage, such as nuclear glycogen deposition, microvesicular steatosis, zone 3 sinusoidal dilatation, patchy hepatic necrosis, and minimal lymphocytic infiltration^[59]. Therefore, in terms of its role in the liver, COVID-19 may worsen liver disease by attacking the remaining parenchyma. Our hypothesis is supported by several Chinese clinical studies that showed that 2% of patients with severe COVID-19 also had HBV infection, in comparison to 0.6% with non-severe SARS-CoV-2 pneumonia^[42,60]. This suggests that patients infected by HBV tend to have a more severe form of SARS-CoV-2. Furthermore, the drugs used to treat COVID-19 are hepatotoxic, which complicates the clinical situation of liver disease patients^[60]. A literature search has not identified any association between fulminant hepatic failure and COVID-19 or that this virus could synergize with factors, such as drugs and viral agents that induce acute liver failure. However, this is due to a paucity of data rather than the effect of the virus. **Table 2** summarizes the clinical data of patients with chronic liver disease that were infected by SARS-CoV-2^[24,42,43,47,48,61,62]. In brief, 2543 COVID-19 patients with a complete medical history (including the severity of disease and outcome) were reported in the literature. Among these patients, 103 had either cirrhosis or HBV-related diseases (4%). Among the patients with cirrhosis, the incidence of severe disease varied between 4.3% to 71.4% in various studies^[24,42,43,47,49,61,62]. Luo and colleagues reported that the mortality rate for COVID-19 patients with pre-existing liver disease was approximately 30%-36%^[61,62]. Therefore, although the incidence of patients with both pre-existing liver disease and COVID-19 is low, their mortality rate is high (close to 40%), which necessitates taking extra precautions for this patient group.

Various societies have recommended that patients with pre-existing liver disease should be managed as follows during the pandemic to reduce the health risks: (1) Postpone outpatient visits for chronic liver diseases that were not hepatocellular carcinoma (HCC) and promote online consultation for these patients; (2) Non-urgent procedures, including elective endoscopy and biopsies, should be postponed; (3) Caring for decompensated cirrhosis, HCC, or transplant patients should continue with the same standards; (4) Always provide protective equipment to protect patients and healthcare workers; and (5) Screen for SARS-CoV-2 when necessary^[63-69]. Special care should be taken when treating SARS-CoV-2 positive patients because the antivirals used to treat COVID-19 are hepatotoxic and interfere with molecules important for liver functions (*e.g.*, cytochrome P450, family 3, subfamily A, CYP A3). Therefore, treatment doses should be reduced for patients with liver disease^[69].

THE IMPORTANCE OF COVID-19 TO LIVER TRANSPLANTATION CENTERS

In this section, we summarize the studies on COVID-19 infection in LT recipients and a living liver donor (LLD)-to-recipient transmission of this virus. D'Antiga^[70]

Table 2 The summary of the clinical studies about coronavirus infectious disease-2019 infection in patients with pre-existing liver disease

Ref.	Total number of Patients	Number of cirrhosis, n (%)	Number severe disease among cirrhosis, n (%)	Number of dismal prognosis among cirrhosis, n (%)
Huang <i>et al</i> ^[24]	41	1 (2.4)	0	0
Guan <i>et al</i> ^[41]	1099	23 (2.1)	1 (4.3)	1 (4.3)
Hu <i>et al</i> ^[43]	323	3 (0.9)	0	0
Cai <i>et al</i> ^[47]	298	28 (9.4)	8 (28.6)	NS
Shi <i>et al</i> ^[49]	81	7 (8.9)	5 (71.4)	NS
Luo <i>et al</i> ^[61]	403	25 (6.2)	NS	9 (36)
Luo <i>et al</i> ^[62]	298	16 (5.4)	NS	5 (31.3)

Dismal prognosis states death ($n = 14$) or progression of the disease ($n = 1$) despite suitable treatment. NS: Not specified.

(Bergamo, Italy), who is from one of the biggest pediatric LT facilities in Europe, commented that, based on his experience with SARS and MERS, LT recipients were not specifically at increased risk from COVID-19. In our opinion, this is a very unfortunate statement based on very premature data. Interestingly, they also showed that of the 700 children treated for various liver diseases, 200 were LT recipients, 3 of these were infected with SARS-CoV-2, and none of them had pneumonia-related symptoms. However, we do not know what happened to these three LT recipients^[70]. We are very interested in their current situation because Italy is now the country with the most COVID-19-related deaths in Europe.

Bhoori *et al*^[71] followed 151 patients who had received LT (111 long-term and 40 short-term LT recipients). In their study, three long-term LT recipients (2.7%) had died from severe COVID-19, and three short-term LT recipients (7.5%) were SARS-CoV-2 positive but had survived the disease. The long-term LT recipients were significantly older (50% of long-term LT recipients and 30% of short-term LT recipients were ≥ 65 years), and were more likely to be obese (80% long-term and 60% short-term), diabetic (60% long-term and 23% short-term), and hypertensive (100% long-term and 68% short-term)^[71]. These pathologies can be attributed to the long-term use of immunosuppressant medications. In a report by Huang *et al*^[72], a 59 years old male patient, who had LT in 2017 to treat HBV-related HCC, was transmitted SARS-CoV-2 by his wife. The clinical picture was complicated by chronic graft rejection, and the patient passed away 26 d later from polymicrobial sepsis. The patient initially developed severe pneumonia, empyema, and pneumothorax, which rapidly progressed to multi-organ failure^[72]. Liu *et al*^[73] reported on a 50 years old male patient who had received a deceased donor LT in 2017 for HBV-related liver failure. The patient developed severe COVID-19 pneumonia 6 d after the onset of symptoms and fully recovered after 2-mo of treatment^[73]. Qin *et al*^[74] reported on a 37 years old male patient who had LT for HBV-related HCC and had traveled to an endemic area and contracted severe COVID-19 during the perioperative period. Fortunately, the patient recovered; however, he was found to be shedding the virus 53 d post-“recovery”^[74]. We believe that LT patients are specifically at risk from COVID-19 and may also be a public health burden because the virus clears at a slower rate from these patients, potentially due to the chronic use of immunosuppressants and therefore these patients may become long-term carriers.

Contrary to D’Antiga^[70]’s report, Lagana *et al*^[75] reported that a 6-mo old infant with biliary atresia, who had received LDLT from her COVID-19-positive mother, was infected *via* this transplant and developed severe pneumonia and hepatitis. A core biopsy obtained on the postoperative seventh day showed infiltration of the portal tracts inflammatory and plasma cells and mild interlobular cholangitis and portal perivenulitis. She was initially treated for T-cell-mediated rejection; however, her illness was aggravated upon increase use of immunosuppressant and subsided once immunosuppression was tapered off. Fortunately, the patient fully recovered^[75], and she did not need intubation.

According to the current literature, a total of 13 COVID-19 patients had undergone LT (assuming that the patients reported by D’Antiga^[70] were post-transplant when they had contracted COVID-19), 7 developed severe pneumonia (53.8%), and 4 died (30.7%) from severe pulmonary infection leading to multi-organ failure^[70-75]. In adults, four out of nine patients with SARS-CoV-2 developed severe pneumonia and had died. A further three patients were asymptomatic carriers who did not develop

symptoms. Four adult LT recipients were short-term liver recipients, and the remaining five were long-term recipients, of which four had died from severe pneumonia and sepsis^[70-75]. There were four pediatric patients, and only one of these had developed severe pneumonia and hepatitis^[70-75]. The published cases are summarized in Tables 3 and 4. In our opinion, these results are alarming, and these patients should have been classified as an at-risk group and should have received regular surveillance for COVID-19 throughout the pandemic. Therefore, the recommendations of certain societies are important when establishing precautionary measures to take in LT centers. In the later part of this section, we will summarize the recommendations from highly respected international and Turkish societies.

Liu *et al*^[69] (Beijing working party for liver transplantation) stated that the LT patients who are permanently on immunosuppressants could be particularly susceptible to SARS-CoV-2, and their prognosis could be worse in comparison to the normal population. This group recommended that both the LLDs and LT recipients should be closely monitored for SARS-CoV-2, including keeping a detailed history of contacts with high-risk individuals. Furthermore, they suggested that all the health personnel and patients should wear protective equipment until the patient is cleared of SARS-CoV-2 risk^[69].

A position paper written jointly by the European Association of the Study of the Liver (EASL) and the European Society of Clinical Microbiology and Infectious Disease (ESCMID) recommended that all patients scheduled for LT should be tested for SARS-CoV-2 and informed of the nosocomial COVID-19 risk^[63]. Furthermore, LDLT should be restricted, and each center should evaluate any operations on a case by case bases. LTs should be restricted to patients with acute or acute chronic liver failure with high model for end-stage liver disease (MELD) scores and HCC patients at the upper limits of the Milan criteria^[63]. The Turkish Association for the Study of the Liver recommended that all elective procedures be postponed, and only emergency operations should be performed provided that the required facilities are available (*e.g.*, a suitable inpatient ward)^[65]. The American Association for Study on Liver Diseases provided similar recommendations: that LT should be limited to emergency cases (*e.g.*, patients with high MELD scores) or HCC patients who are at risk of disease progression and removal from the waiting list^[64]. The Turkish Surgical Society recommended that all elective and laparoscopic procedures be canceled^[76]. Urgent procedures should be performed under strict isolation conditions for the staff in a well-ventilated laminar flow-equipped operating room and only minimal number of personnel and equipment allowed^[76]. The LT society of India (LTSI) highlighted the potential of LT recipients as asymptomatic carriers and source of viral spread^[77], and that SARS-CoV-2 can be transmitted from LLDs to LT recipients. In addition, they stated that a longer hospitalization period for these patients increases the risk of nosocomial viral spread since the hospitals have many COVID-19 patients. The LTSI recommended that elective procedures be postponed, and both deceased donors and LLDs be tested for SARS-CoV-2. Only emergency procedures for acute and acute-on-chronic liver failure should be performed, and general hospital visits for patients on surveillance should be limited^[77]. The British Association for the Study of the Liver and British Liver Transplant Group sent out a joint statement recommending that all LT recipients should take the necessary precautions to reduce the spread of SARS-CoV-2, which includes using protective equipment and frequent handwashing^[78]. Furthermore, they suggested limiting hospital visits, unless in the event of a medical emergency^[78].

There are insufficient data on the relationship between immunosuppressive therapy and COVID-19 in LT recipients during this pandemic. However, the Beijing working party for liver transplantation suggested that LT recipients who were infected with SARS-CoV-2 should be treated with steroids for a short period to reduce the severity of pneumonia^[69]. They also suggested that immunosuppressive therapies should be continued for both patients with mild COVID-19 and those who were not infected by the virus, and calcineurin inhibitor treatment dosage should be reduced in moderate to severe cases^[69]. In contrast, the EASL-ESCMID position statement suggested that the immunosuppressive medication dosage could be adjusted according to the antiviral treatment protocols because there is a high chance that the drugs from both treatment protocols could interact^[63].

There is very limited data for LT recipients, and the effectiveness of the above societies' recommendations is unknown. Our LT institute is classified as a center of excellence for LDLT, and we perform 250 to 300 LT annually. We have performed 35 LDLT (34 semi-urgent and 1 emergency) procedures since the first Turkish COVID-19 case on March 11, 2020, of which 4 were pediatric patients and 31 were adult recipients. We routinely test LLD candidates and their LT recipients for SARS-CoV-2 by nasopharyngeal swabs before LT surgery. Furthermore, we repeat the same test before discharging the patients. We have not encountered a SARS-CoV-2-positive LT

Table 3 The summary of the reported case series of coronavirus infectious disease-2019 in liver transplant recipients

Ref.	Total No. of transplants	Age group	Date of LT procedure	No. of COVID-19 cases, <i>n</i> (%)	No. of deaths, <i>n</i> (%)
D'Antiga ^[70]	700 ¹	Pediatric	NS	3 (0.04)	0
Bhoori <i>et al</i> ^[71]	151	Adult	111 (> 10 yr) vs 40 (< 2 yr)	6 (3.9)	3 (1.9) ²

¹D'Antiga^[70] reported the total number of pediatric patients with the liver disease treated in their institute. Seven hundred patients include 200 liver transplant recipients as well. They have not specified the 3 patients with coronavirus infectious disease-2019 (COVID-19); whether they are a transplant recipient or not is unknown.

²The three transplant recipients that died due to COVID-19 were from the long-term recipient group. The graft types were not specified in both studies. No.: The number of affected individuals; COVID-19: Coronavirus infectious disease-2019.

recipient or donor, and none of our patients exhibited severe COVID-19 pneumonia. We have limited the number of patients in our outpatient clinic and only performed LT for cases that were of urgent need. We took the necessary precautions for our healthcare personnel by limiting the duration of patient interaction and providing protective equipment to everyone, including the inpatients. These precautions appear to be useful in reducing the number of cases. However, we should approach with caution when we make such a statement because that there is still a long time ahead of us and the disease is still spreading in Turkey.

CONCLUSION

COVID-19 is the cause of a worldwide tragedy. These are unprecedented times that a healthcare provider hopes that he or she will never encounter throughout their career. It has limited our social life, dictated the way we work, and has resulted in a very isolated and limited lifestyle. Unfortunately, as healthcare providers, we have to take care of patients with COVID-19 and also continue our professional and social activities. We belonged to a sub-specialty that deals with a terminally ill patient group. The data suggest that patients with liver disease and transplant candidates are particularly at risk from COVID-19. We are still a long way from having a definitive treatment or vaccine. We are faced with treating a deadly infection in a very susceptible group; therefore, we, the healthcare providers, should have an understanding of the disease, should be able to take the necessary precautions to ensure the safety of both our patients and ourselves. Furthermore, we should be ready for the worst and prepare our institution accordingly. Prevention is the best treatment; therefore, we should try to protect our patients from being infected by postponing non-priority procedures or visits to the hospital. Telemedicine could be used to monitor patients, and online platforms could be set up for patients to discuss their health status with physicians. If prevention is impossible, isolation techniques should be employed by both staff and patients, routine SARS-CoV-2 surveillance should be performed, and the facility should be arranged to manage these patients accordingly.

Table 4 Summary of single case reports of coronavirus infectious disease-2019 in liver transplant recipients

Ref.	Sex	Age	LT date	Type of LT	Etiology	Duration before diagnosis (d)	Severity of COVID-19	Outcome	Time to outcome (d)
Huang et al ^[72]	M	59	2017	NS	HBV+HCC	3	Severe	Died	45
Liu et al ^[73]	M	50	2017	DDLT	HBV	6	Severe	Recovered	38
Qin et al ^[74]	M	37	2019	NS	HBV+HCC	9	Mild	Recovered	53
Lagana et al ^[75]	F	0.5	2020	LDLT	Biliary atresia	0 ¹	Severe	Recovered	NS ²

¹Lagana and colleagues have reported a pediatric living donor-recipient who contracted the virus from the donor (mother of the patient). The donor was tested positive on post-transplant day 2 and the patient was diagnosed on postoperative day 4 due to difficulty in breathing.

²The patient was still hospitalized with very minor respiratory symptoms. LT: Liver transplant; DDLT: Deceased donor liver transplant; LDLT: living donor liver transplantation; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; M: Male; F: Female; NS: Not specified; COVID-19: Coronavirus infectious disease-2019.

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