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Impact and management of COVID-19 in liver transplant candidates and recipients

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Abstract

The COVID-19 outbreak has had severe consequences for global public health, medical communities, and the socioeconomic status of a considerable number of countries. The emergence of COVID-19 has also significantly impacted the world of liver transplantation (LT). Studies from transplantation centers around the world have shown that LTs during the COVID-19 pandemic have been restricted because of the high risk of serious COVID-19 infection in this population. According to the Centers for Disease Control and Prevention, patients with liver disease are considered at higher risk for severe COVID-19 infection. In March 2020, the American Association for the Study of Liver Diseases recommended that LT should be limited to emergency cases. The COVID-19 treatment guidelines published by the National Institutes of Health are being constantly updated according to new epidemiology trends and treatment regimens. Immunocompromised patients have a higher risk of developing severe disease or death from COVID-19 compared with the general population. In this review, we summarize the available evidence regarding treatment guidelines and considerations for the evaluation and management of LT candidates and recipients in the era of COVID-19. In addition, we present data regarding COVID-19 among LT patients in our local transplantation center.

Keywords COVID-19, SARS-CoV-2, liver transplantation, chronic liver disease, vaccination

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Introduction

COVID-19 is an infectious disease caused by SARS-CoV-2 virus [1]. COVID-19 was first reported in December 2019 in Wuhan, the capital city of Hubei province in China, as pneumonia cases of unknown etiology [2]. A month later (January 2020), this novel coronavirus was officially identified by the Chinese Center for Disease Control and Prevention, and subsequently the World Health Organization publically declared it a global emergency [3,4]. Rapidly, the disease spread from China to other areas worldwide and developed into a pandemic in March 2020 [1,6]. The COVID-19 outbreak has had severe consequences for global public health, medical communities, and the socioeconomic status of a considerable number of countries [5]. Since the COVID-19 pandemic started, over 2 million people in the European region have died from the disease [6].

Management of COVID-19 in liver transplant (LT) recipients can be challenging because of the presence of comorbidities, the risk of transplant-related cytopenias, and the impaired immune system as a result of immunosuppressive therapy. Furthermore, LT candidates and recipients are at greater risk of being exposed to SARS-CoV-2, as they must visit healthcare facilities frequently [7]. The American Association for the Study of Liver Diseases (AASLD) provides recommendations for clinicians who are caring for LT recipients with COVID-19, as well as patients with chronic liver disease (CLD) awaiting LT [8,9].

In this review, we summarize the available evidence related to treatment guidelines, and considerations for the evaluation

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and management of LT candidates and recipients in the era of COVID-19. In addition, we present data regarding COVID-19 in LT recipients in our local LT center in Thessaloniki, Greece.

COVID-19 and LT candidates

Course of COVID-19 in LT candidates

Cirrhotic patients experience immune dysfunction and are consequently at greater risk for infections and associated complications, which may result in acute decompensation and early death if LT is not performed promptly [10,11]. According to published data, the 60-day mortality risk of LT candidates with decompensated cirrhosis (DC) and COVID-19 during the first wave (35.3%) did not significantly decline during the second wave of the pandemic (26%) [12]. Observational studies confirmed that cirrhotic patients infected by SARS-CoV-2 tend to have a poor prognosis and higher mortality rates compared to non-cirrhotic patients [13,14]. There is evidence that lower platelet and lymphocyte counts, hypoproteinemia, higher bilirubin levels, any increase in the Child-Pugh score, and acute-on-chronic liver failure (ACLF) might be indicators of poor prognosis and higher mortality risk in CLD patients infected by SARS-CoV-2 [15,16]. A study of cirrhotic patients with COVID-19 showed that almost 46% developed acute decompensation or worsening of pre-existing DC [17]. It is interesting that, in most of these patients (20-58%), decompensation occurred in the absence of respiratory symptoms of COVID-19 [14,17,18]. They more frequently developed gastrointestinal symptoms, probably due to impaired gut permeability and systemic inflammation, associated with a worse disease outcome [17,19,20].

In a multicenter European cohort study, symptomatic patients with SARS-CoV-2 infection listed for LT were found to be at greater risk of early death (33%), particularly those with DC and model for end-stage liver disease (MELD) score ≥15 (49% mortality rate, which is 3 times that observed in listed patients with comparable MELD score without COVID-19) [12,21]. Furthermore, it was noted that the prevalence of COVID-19 in LT candidates was 6.05%, which is twice that observed in the general population of similar age, probably because of those patients' higher susceptibility to SARS-CoV-2 infection [19]. The mortality risk was even greater in those with dyspnea on presentation. Respiratory failure was the most frequent cause of death (89%) [12]. Based on the above, the AASLD recommended that, in order to minimize inpatient and outpatient visits, patients with CLD awaiting LT should follow all preventive measures against SARS-CoV-2 infection, as well as the vaccination schedule [22].

Published data have shown that cirrhotic livers have a >30-fold greater expression of angiotensin-converting enzyme 2 (ACE-2) receptor, indicating that cirrhotic patients may have a higher susceptibility to SARS-CoV-2-mediated hepatic dysfunction [23]. Studies revealed clear evidence of specific SARS-CoV-2 hepatotropism, explaining the fact that the virus triggers decompensation in patients with pre-existing CLD [18]. ACLF after SARS-CoV-2 is reported in up to 12-50% of patients with DC [13,14,17]. However, the most frequent cause of death among cirrhotic patients remains respiratory failure (71%), followed by liver-related complications (19%) [17]. Mechanistic links between hepatic dysfunction and subsequent lung injury, including cirrhosis-associated immune dysfunction, gut dysbiosis, altered pulmonary dynamics secondary to ascites, hepatic encephalopathy, and coagulopathy, explain the causative relationship [18,24]. Higher rates of pulmonary emboli in patients with CLD have also been noted, contributing to greater mortality rates [25].

LT candidates with COVID-19 showed a 30-day mortality probability similar to that observed in cirrhotic patients hospitalized for acute decompensation due to bacterial infections. Notably, it was found that patients who had recovered from COVID-19 could be safely transplanted, with excellent short-term survival (96%) and no cases of SARS-CoV-2 reinfection. To undergo LT, all COVID-19-infected LT candidates had to be asymptomatic, with a minimum of 1 negative reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal swab and an additional negative swab at the time of LT [12]. However, the ideal disease-free interval before LT is still unclear. An international, multicenter, prospective cohort study found that any type of surgery performed ≥7 weeks after SARS-CoV-2 diagnosis was associated with similar mortality risk compared to those without previous SARS-CoV-2 infection. Patients with ongoing symptoms for ≥7 weeks had a higher mortality risk than those without, or with resolved symptoms [26]. Thus, it is recommended that LT candidates should have complete symptom resolution and, ideally, a negative SARS-CoV-2 PCR from the respiratory tract prior to LT [27].

The clinical characteristics of COVID-19 may vary between patients with CLD and different pre-existing causes. Nonalcoholic fatty liver disease (NAFLD) is often associated with comorbidities, such as hypertension, diabetes and obesity, that have been documented as independent risk factors for a poor prognosis of COVID-19 [28]. In addition, NAFLD patients may have a longer viral shedding time, a higher possibility of liver dysfunction and a greater risk of severe COVID-19, compared to non-NAFLD patients. As a result, NAFLD was recognized as an independent risk factor for severe COVID-19 [29,30]. On the other hand, dysfunction of the immune system caused by alcohol intake may increase the risk of severe COVID-19 in patients with alcoholic liver disease (ALD). Furthermore, patients diagnosed with hepatocellular carcinoma (HCC) and COVID-19 were found to have an all-cause mortality rate of 52.4%, almost 7 times greater than that of patients without HCC. Most patients with HCC have underlying cirrhosis, which means that they have 2 independent factors for poor prognosis of COVID-19 [19].

Impact of COVID-19 on LT volume

LT programs worldwide have been deeply affected by the outbreak of the COVID-19 pandemic. Solid organ

transplantation (SOT) has decreased even in regions where COVID-19 prevalence was low, which suggests a global and nationwide effect beyond the local COVID-19 prevalence. The overall reduction in deceased donor transplantations since the COVID-19 outbreak was 90.6% in France and 51.1% in the USA, respectively [31]. Furthermore, professional associations of hepatology and transplant providers in different countries around the world recommended limitation of LTs in response to the COVID-19 pandemic. More specifically, the European Association for the Study of the Liver and the European Society of Clinical Microbiology and Infectious Diseases recommended that LTs should be limited: each center should evaluate any operations on a case-by-case basis, giving priority to patients with acute liver failure or ACLF with high MELD scores, as well as HCC patients at the upper limits of the Milan criteria [32]. The AASLD recommended that LT should be limited to emergency cases (such as patients with high MELD scores), or HCC patients who are at risk of disease progression and removal from the waiting list [33,34].

Currently, 10,864 patients are included on the national waiting list for LT in the USA [35]. Before the COVID-19 pandemic, overall wait-list mortality was 13.2 per 100 wait-list years, with a greater mortality rate observed in patients aged ≥65 years [36]. During the COVID-19 pandemic, many LT centers around the world stepped down their transplant activity as COVID-19 cases rose, because of inadequate resources, and also because of the risk of nosocomial spread, factors that were considered to outweigh the benefit of performing an LT [37]. Data from the United Network for Organ Sharing revealed a significant decline in both living and deceased donor LT, an increase in wait-list inactivation and a decrease in the utilization of deceased-donor organs [38]. In our LT center in Thessaloniki Greece, referrals also decreased significantly, resulting in a sharp decline in the total number of transplants, as summarized in Fig. 1. Most patients and their relatives avoided visiting healthcare facilities for fear of contracting COVID-19. Consequently, many healthcare procedures were postponed.

During the COVID-19 pandemic, LT programs were also impacted by alcohol consumption. Harmful drinking rose significantly, while the purchase of alcoholic beverages increased by as much as 400% [39,40]. Furthermore, 17% of abstinent patients with a history of alcohol use disorder relapsed under lockdown conditions [41]. Currently, ALD accounts for 40% of transplant listings in North America, more than nonalcoholic steatohepatitis and chronic hepatitis C combined. The severity of liver disease at the time of LT was worse, with higher MELD scores during the COVID-19 pandemic [42]. Lockdown conditions resulted in patients following a harmful lifestyle, with reduced physical activity, excess calorie intake, and consumption of unhealthy foods. Thus, an increased prevalence of obesity and NAFLD was also observed [18,43,44].

Regarding the outcome of surgical procedures that were performed during the COVID-19 pandemic, published data revealed that LT patients infected with SARS-CoV-2 who underwent surgery experienced significant postoperative morbidity and mortality [45]. In a large international study of SARS-CoV-2-infected patients who underwent emergent or elective nontransplant surgeries, the 30-day mortality was found to be 21%, with nearly half of those patients developing pulmonary complications [46]. Surgical stress can lead to a cytokine release syndrome, resulting in severe complications, such as superimposed infections and graft loss [47]. Active SARS-CoV-2 infection in the early postoperative period may be complicated by arterial or venous thromboses, myocarditis or myocardial infarction, renal failure or respiratory failure [8,48,49]. Furthermore, SARS-CoV-2 infection can cause acute hepatitis (reference to SARS-CoV-2 in biopsy) with an elevation of transaminases up to 3 times the upper limit of normal, while in some cases it can progress to acute liver failure [8,50]. Thus, distinguishing acute rejection from viral-induced hepatitis in LT patients could be challenging [8].

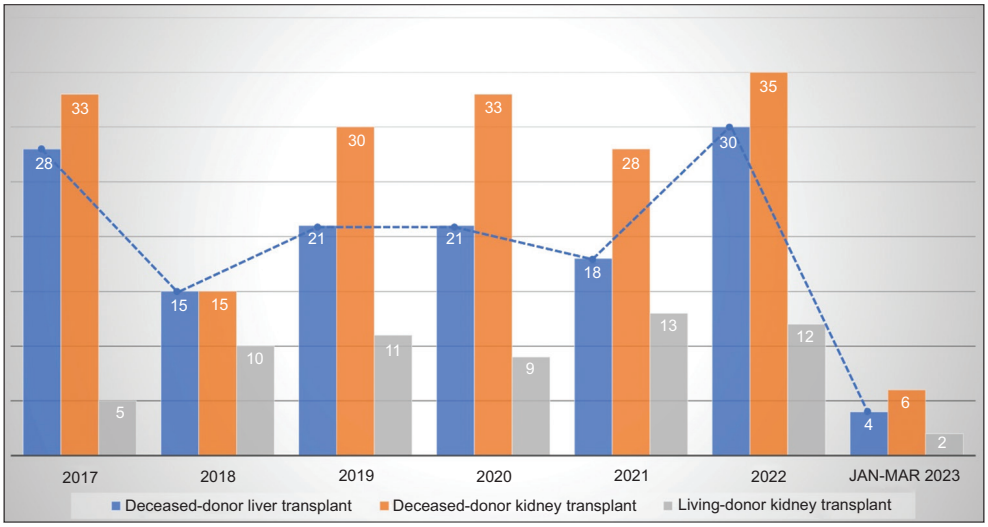

Figure 1 Solid organ transplantations performed in the Transplantation Center in Thessaloniki Greece

Vaccination guidance against COVID-19

Vaccination against COVID-19 remains the first line of prevention and the most successful method of preventing SARS-CoV-2 infection. Considering the effectiveness of COVID-19 vaccines in the general population and the high risk of worse clinical outcomes of COVID-19 in LT candidates and recipients, vaccination against COVID-19 is strongly recommended for these patients [33,51]. Recently, in a retrospective study of US veterans with cirrhosis, the acquisition of at least one single mRNA vaccine dose resulted not only in lower rates of SARS-CoV-2 infection, but also in significantly lower rates of hospitalization and mortality among these patients [52]. In immunocompromised patients vaccine response rates may be lower, and specific guidance on administering vaccines is provided by the Centers for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices, as demonstrated in Fig. 2 [18,51,53]. Furthermore, it is strongly recommended that all individuals who have close contact with LT recipients and donors should be vaccinated against COVID-19 [51].

Clinical trials that assessed the safety and efficacy of COVID-19 vaccines excluded severely immunosuppressed patients [54-56]. However, the currently authorized COVID-19 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised individuals [57]. Clinical studies revealed that SOT recipients have lower immunological antibody responses following a primary 2- or 3-dose series of the messenger ribonucleic acid (mRNA) COVID-19 vaccines [58,59]. Ideally, SOT candidates should complete the whole vaccination schedule against SARS-CoV-2 infection while they are awaiting LT. Vaccination should be completed at least 2 weeks before LT or should be started 1 month after LT. According to the NIH treatment guidelines for COVID-19, it is not recommended to reduce the dose or withhold immunosuppressive therapy before COVID-19 vaccination in an attempt to improve seroconversion rates [18]. After vaccination, immunocompromised patients should strictly follow all preventive measures against COVID-19 (such as wearing a mask or avoiding crowds) [60]. Post-vaccine serologic testing for immunity against SARS-CoV-2 in immunocompromised patients is not recommended because of insufficient data [18].

Clinical studies revealed that the immune reaction of LT recipients to COVID-19 vaccination was reduced, as neutralizing antibodies were detected in only 47.5% of the included LT patients (n=80). Also, seroconversion and the T-cell response rates to the second SARS-CoV-2 vaccination in LT patients were only 63% and 36.6%, respectively, while 28% showed no response [61]. On the other hand, in patients with liver cirrhosis, the serum conversion rate after the second vaccination reached almost 100% [62]. Patients with liver cirrhosis (with or without HCC), as well as patients awaiting LT, should be fully vaccinated (third or even fourth booster) [63]. However, there are still limited data regarding the duration of vaccination protection for CLD patients, LT candidates and recipients.

In LT transplant candidates or recipients who do not have an adequate protective response to COVID-19 vaccines, anti-SARS-CoV-2 monoclonal antibodies (mAbs) with tixagevimab plus cilgavimab are recommended as pre-exposure prophylaxis (medication designed to block COVID-19 from attaching to and entering human cells, thus protecting them from being infected) in specific settings. Patients should not have ongoing SARS-CoV-2 infection or recent exposure to COVID-19 to receive the pre-exposure prophylaxis [18,33,51]. In a recently published phase III trial, tixagevimab plus cilgavimab administration was associated with a lower incidence of symptomatic and severe COVID-19 disease among infected participants (relative risk reduction of 82.8%, 95% confidence interval [CI] 65.8-91.4). Pharmacokinetic data showed the persistence of the monoclonal-antibody combination in serum for 6 months after administration [64]. The American Society of Transplantation (AST) and the AASLD recommend giving

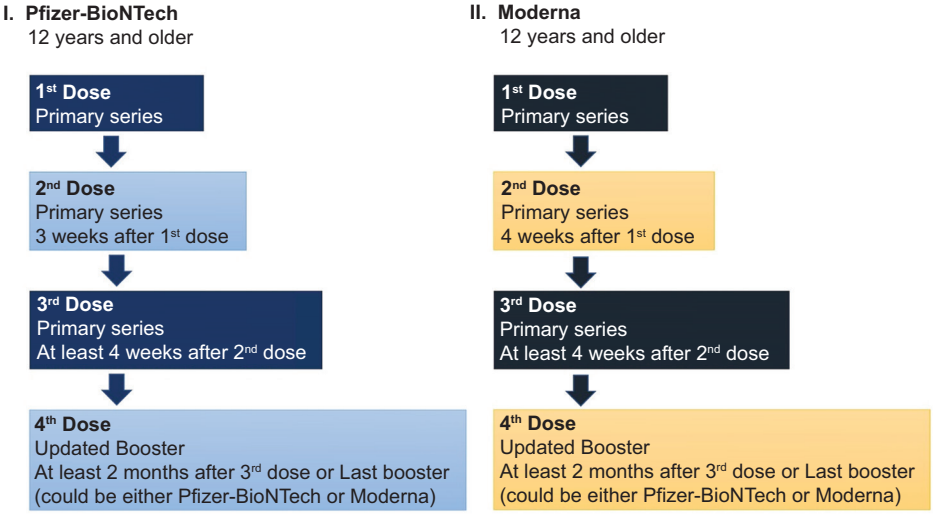

Figure 2 Vaccination schedule against COVID-19 for immunocompromised patients

the COVID vaccine first, to stimulate host T-cell immunity, and then administering tixagevimab plus cilgavimab at least 14 days after the last COVID vaccine dose. However, it should be used with caution in patients with heart disease. All of the patients with a cardiac adverse event had a known heart condition (heart failure exacerbation, atrial fibrillation development) [65].

Guidance for COVID-19-positive donors

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability of a donor or candidate being infected by SARS-CoV-2 can be estimated by taking into consideration the epidemiologic risk and testing with RT-PCR. Unfortunately, no current test is sensitive enough or specific enough to exclude active SARS-CoV-2 infection. The NIH recommend performing RT-PCR testing for SARS-CoV-2 for all SOT candidates and donors with signs and symptoms compatible with acute COVID-19. They should be assessed for exposure to COVID-19 before they are called in for LT, and should undergo RT-PCR testing for SARS-CoV-2 shortly before LT. If SARS-CoV-2 is detected, or if infection is strongly suspected, transplantation should be deferred [51].

The optimal disease-free time interval before LT is not known. When considering the optimal timing for transplantation, clinicians should consider both the risk of viral transmission and the risks to the candidate if the transplant is deferred. Living solid organ donors should be counseled to prevent infection and should be monitored for exposures and symptoms in the 14-day period before the scheduled transplantation [66]. Furthermore, they should undergo RT-PCR testing for SARS-CoV-2, with a sample collected within 3 days of donation. Deceased donors should be tested for SARS-CoV-2 infection using an RT-PCR assay of a sample taken from the upper respiratory tract within 72 h of death [67,68].

COVID-19 and post-LT patients

Pathogenesis of COVID-19 in LT patients

Under normal conditions, the entry of SARS-CoV-2 into the host generates a robust immune response that involves components of both innate and adaptive immunity. First, an interferon (IFN)-based response is elicited, which, in conjunction with the recruitment of major elements of innate immunity, such as neutrophils and tissue macrophages, serves as means of halting virus propagation. Following this series of events, viral antigen presentation via antigen-presenting cells results in the activation of CD8+ T-cells, which directly target the virus, and CD4+ T-cells, which promote B-cell activation and antibody production [69]. SARS-CoV-2, however, can evade the immune responses intended to prevent its spread. IFN production is hampered during SARS-CoV-2 infection, most likely because of a decrease in the transcription of associated genes that code for such proteins, resulting in a diminished innate response. At the same time, the virus can reduce the number of effector T-cells, which are responsible for coordinating the adaptive immune response to infection. These mechanisms allow the virus to replicate, while at the same time, the exaggerated cytokine release that is observed during SARS-CoV-2 infection is responsible for many detrimental outcomes of severe infection, such as acute respiratory distress syndrome [70].

Immunosuppressed individuals experience alterations in their innate and adaptive immunity, that inevitably place them at higher risk for infection. Immunosuppressants inhibit T-cell production or block T-cell action. This mechanism negates the defensive role of adaptive immunity during SARS-CoV-2 infection. Approaches that serve to minimize this risk usually focus on reducing the immunosuppressant dose, withholding the medication, or switching to a different class of drug. This is because the immune response to infection is not always the same, but seems to change dynamically according to the type of immunosuppressant used after SOT, regardless of the clinical significance this may have for the outcome of the infection [71].

Course of COVID-19 in LT patients: data from international studies

Several observational studies that recruited LT recipients infected with SARS-CoV-2 aimed to find out the epidemiological profile, infections, clinical spectrum, prognosis, treatment approaches, and complications associated with COVID-19. A study performed in >80 major transplant centers in the USA between March 24 and March 31, 2020, revealed 148 SOT patients infected by SARS-CoV-2 in 31 (35.2%) centers. Mild disease was reported in 80 patients (54.1%), 31 (20.9%) patients had moderate disease with pneumonia, and 37 (25.0%) were critically ill. In this study, greater disease severity was found in patients with SOT infected by SARS-CoV-2 compared to those without SOT and COVID-19 [37]. Furthermore, clinical studies revealed that SOT recipients infected by SARS-CoV-2 may shed greater amounts of virus, for longer durations, than non-immunocompromised patients [72].

Another multicenter observational cohort study in the United States identified 112 LT recipients with COVID-19. The overall mortality rate was 22.3% and, of the 81 patients hospitalized, 37% were admitted to the Intensive Care Unit. Predictors of liver injury and mortality included race (White), ethnicity (Hispanic), metabolic syndrome, antibiotic and vasopressor administration, previous liver disease, diabetes mellitus, hypertension, and active cancer. Although changes in immunosuppression were not associated with different outcomes during infection, modifications to the regimen were made in 49.4% of the patients, mainly withholding mycophenolate mofetil (MMF) or decreasing the dose of tacrolimus [73]. An additional retrospective study analyzed 243 LT recipients with COVID-19 and found a mortality rate of 20.2%. Negative predictors of mortality and liver injury were age >70 years, diabetes, chronic kidney disease, and time

between LT and COVID-19 symptoms. Notably, the use of tacrolimus had a positive impact on survival [74]. Additional studies reported similar findings, as demonstrated in Table 1.

Based on the above, the presence of comorbidities, such as diabetes, hypertension, metabolic syndrome, chronic kidney disease, active cancer, as well as advanced age, in LT recipients seems to be more highly correlated with a poor prognosis following SARS-CoV-2 infection than the type of immunosuppressant used, or the change made to the regimen. In other words, it appears that the state of immunosuppression *per se* is not an independent risk factor for negative outcomes following viral infection, but rather, the individual's disease profile seems to determine infection severity and outcome [73,74,76-79].

Next, the mortality rate observed in most of the above studies did not differ when compared to the mortality rate reported in the general population [73,74,77], although some studies reported lower [75,76,78] or higher mortality [79,80]. This observation reinforces the statement that LT alone may not account for the negative outcomes observed in this population group. Similar mortality rates have also been observed in SOT recipients as a whole and the general population [86,87]. Rates of hospital admission, however, were higher in LT recipients in some studies [77,79,86]. This may reflect a biased approach to SOT recipient management out of fear of severe infection due to their immunosuppressed status.

Regarding symptoms at the time of diagnosis, respiratory complaints, such as dyspnea and cough, did not differ between the SOT recipients and the general population. The presence of gastrointestinal symptoms, however, such as vomiting, diarrhea, and abdominal pain, was significantly higher in LT recipients; thus, a thorough clinical assessment is warranted when examining these patients for possible SARS-CoV-2 infection [74,76,79,80]. Finally, liver injury is of special concern, since the viability of the transplanted graft depends on adequate liver function. ACE-2 receptors, utilized by the

Table 1 Studies evaluating SARS-CoV-2 infection in LT recipients

Study [ref.]	Type of Study	Number of LT recipients	Mortality rate (%)	Hospital admission rate (%)	ICU admission rate (%)	Independent mortality risk factors**
Rabiee *et al* [73]	Multicenter single-arm	112	22.3	72.3	26.8	Liver injury, DM, HTN, active cancer
Belli *et al* [74]	Multicenter single-arm	243	20.2	85	15.2	Age >70 years, time from LT, CKD, number of comorbidities, use of TAC
Colmenero *et al* [75]	Prospective single-arm	111	18	86.5	10.8	Use of mycophenolate
Webb *et al* [76]	Multicenter cohort	151	19	82	28	Increased age, non-liver cancer, high baseline serum creatinine
Mansoor *et al* [77]	Multicenter cohort	126	8	40	8	N/A
Fraser *et al* [79]	Systematic review	223	19.3	77.7	N/A	Age >60 years, DM, dyspnea at diagnosis
Bhoori *et al* [78]	Single-center, single-arm	111	3	N/A	N/A	N/A
Webb *et al* [16]	Observational	39	10.2	N/A	N/A	N/A
Lee *et al* [80]	Single-center single-arm	38	18	71	33	N/A
Becchetti *et al* [81]	Prospective single-arm	57	12	65	7	History of cancer, lymphopenia
D'Antiga *et al* [82]	Case series	700	0	0	0	N/A
Waisberg *et al* [83]	Case series	5	20	100	N/A	N/A
Huang *et al* [84]	Case report	1	100	100	100	N/A
Lagana *et al* [85]	Case report	1	0	100	100	N/A

*Studies with only LT recipients were included in the table

**Refers to risk factors that were significantly associated with mortality from SARS-CoV-2 infection, either positively or negatively

LT, liver transplantation; ICU, intensive care unit; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; TAC, tacrolimus; N/A, not applicable

virus, are found in bile duct epithelial cells. This would explain a cholestatic pattern of liver injury induced by the virus [88]. In the LT setting, a study of 112 patients revealed that 65.4%, 22.2% and 12.3% of patients had alanine aminotransferase (ALT) levels <2, 2-5 and >5 times the upper limit of normal (ULN), respectively. In this study, the primary pattern of liver injury was hepatocellular rather than cholestatic. The study also found that younger age, Hispanic ethnicity, metabolic syndrome, receipt of vasopressors, and antibiotic use were independent risk factors for liver injury [79].

When evaluating SARS-CoV-2-induced liver injury, drug-mediated hepatotoxicity has to be taken into account. Of the antiviral drugs used to treat SARS-CoV-2 infection, remdesivir and tocilizumab are associated with elevated liver enzymes. Although their contribution to liver injury has not been substantiated in studies, it is reasonable to avoid these medications in LT recipients with laboratory evidence of liver dysfunction and ALT >5 times the ULN [88]. Other drugs, such as antibiotics, used either to treat infections or prophylactically in the post-LT setting, may also cause liver injury. Overall, liver damage, which may present with variable patterns of liver injury, is an independent risk factor for increased mortality in LT recipients and may represent either a direct effect of the virus on hepatocytes and cholangiocytes or a consequence of other variables, namely hepatotoxic medications and infection [73,89].

LT center experience in Thessaloniki, Greece

In our LT center in Thessaloniki, Greece, we performed a retrospective analysis that included 37 LT patients infected with SARS-CoV-2 from February 2020 until January 2022. The mean age of our patients was 56.86±14.49 years, with a male predominance (56.8%) and a mean time from LT of 12.11±7.80 years. The most common comorbidities were arterial hypertension (30.6%) and diabetes mellitus (22.2%). The most frequent indication for LT was chronic hepatitis B (35.1%). Regarding immunosuppressive therapy and treatment regimens used for COVID-19, data are summarized in Table 2.

We found that 19 patients (54.3%) were vaccinated against SARS-CoV-2, of whom 14 were fully vaccinated with 3 vaccine doses at the time of infection, with a significantly reduced risk for hospitalization (40%, odds ratio [OR] 0.10, 95%CI 0.01-0.95; P=0.45). Almost one-third of LT patients (n=10) needed hospitalization, and of these 87.5% were unvaccinated against SARS-CoV-2, with an almost 10-fold increased risk for hospitalization (OR 10.11, 95%CI 1.05-97.00; P=0.07). Fever and cough were the main symptoms (60.6% and 51.5%, respectively), whereas 30.3% of patients presented with gastrointestinal symptoms having an almost 16-fold increased risk for hospitalization (OR 15.75, 95%CI 2.30-107.93; P=0.05). Most patients recovered from COVID-19 uneventfully. Only 1 death occurred during hospitalization, and this was thought to be unrelated to the SARS-CoV-2 infection. The majority of hospitalized patients (80%) were over 60 years old (P=0.057). Six hospitalized patients, 83.3% of whom were over 60 years old, received supplemental oxygen therapy. None of the LT patients required mechanical ventilation.

Guidance for the management of COVID-19 in LT patients

The COVID-19 treatment guidelines published by the NIH are being constantly updated according to new information about the *in vitro* susceptibility of the emerging SARS-CoV-2 variants of concern to treatment regimens [90]. Several therapeutic regimens are available to treat non-hospitalized immunocompromised patients with mild to moderate COVID-19. The selection of the appropriate regimen must take into account its clinical efficacy and availability, the feasibility of administering parental medications, the potential for significant drug–drug interactions, and the regional prevalence of variants of concern. Symptomatic treatment with antipyretics, analgesics, or antitussives is recommended for all patients [91]. The CDC recommends that immunocompromised patients should be quarantined for 10 days after COVID-19 diagnosis [95].

Immunocompromised patients with mild or moderate COVID-19 should receive antiviral drugs (ritonavir-boosted nirmatrelvir, remdesivir, bebtelovimab, and molnupiravir). Ritonavir-boosted nirmatrelvir (Paxlovid®) is recommended for use in most high-risk non-hospitalized patients with mild to moderate COVID-19. If ritonavir-boosted nirmatrelvir is not available or cannot be administered because of drug–drug interactions, remdesivir is recommended as a second option. Bebtelovimab and molnupiravir are recommended as alternative therapy choices, and should only be administered when neither of the first-line treatment options is available, feasible to use, or clinically appropriate [51]. Dexamethasone or other systemic glucocorticoids are recommended to be used for the treatment of outpatients with mild to moderate COVID-19 [91]. However, observational studies have shown that the use of corticosteroids in LT patients may increase the risk of infections. Thus, it is recommended to use corticosteroids with caution in LT patients, preferably if minimal supplemental oxygen is needed [92]. It should be noted that oral corticosteroid therapy used before the COVID-19 diagnosis should not be discontinued. Anticoagulation therapy can be administered, even for non-hospitalized patients [8,91]. Finally, it is recommended to continue receiving drugs prescribed for comorbid conditions, as directed by the physician [91].

Clinicians should be aware of the potential drug–drug interactions and overlapping toxicities between treatment regimens for COVID-19 and concomitant medications. Adjustment of the immunosuppressive therapy should be individualized based on COVID-19 severity, the type of immunosuppressants, the type of transplant, the time since transplantation, and the risk of graft rejection [51]. Calcineurin inhibitors (cyclosporine, tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus) have a narrow therapeutic index. Medications that inhibit or induce cytochrome P450 (CYP) enzymes or P-glycoprotein may result in clinically significant drug–drug interactions,

Table 2 Clinical characteristics of hospitalized and non-hospitalized LT patients with COVID-19 in our liver transplantation center in Thessaloniki, Greece

Clinical characteristics % (n/N)		All LT patients	Hospitalized	Non-hospitalized	P-value
Demographic characteristics	Age (Mean)	56.86±14.49	63.10±12.12	54.56±14.81	0.057
	Gender (Male)	56.8 (21/37)	60.0 (6/10)	55.6 (15/27)	>0.99
	HTN	30.6 (11/36)	50.0 (5/10)	23.1 (6/26)	0.224
	DMII	22.2 (8/36)	20.0 (2/10)	23.1 (6/26)	>0.99
	Obesity	29.4 (10/34)	33.3 (3/9)	28.0 (7/25)	>0.99
	Years from LT (Mean)	12.11±7.80	10.90±7.74	12.56±7.92	0.095
Vaccination status	Unvaccinated	45.7 (16/35)	87.5 (7/8)	33.3 (9/27)	0.007
	2 doses	14.3 (5/35)	0.0 (0/8)	18.5 (5/27)	0.999
	3 doses	40.0 (14/35)	12.5 (1/8)	48.1 (13/27)	0.045
Indication for LT	HBV	35.1 (13/37)	40.0 (4/10)	33.3 (9/27)	0.716
	HCV	16.2 (6/37)	30.0 (3/10)	11.1 (3/27)	0.313
	HCC	18.9 (7/37)	20.0 (2/10)	18.5 (5/27)	>0.99
	Alcoholic	13.5 (5/37)	30.0 (3/10)	7.4 (2/27)	0.110
	NASH	8.1 (3/37)	0.0 (0/10)	11.1 (3/27)	0.548
	Autoimmune (AIH, PBC)	18.9 (7/37)	20.0 (2/10)	18.5 (5/27)	>0.99
	Other	21.6 (8/37)	10.0 (1/10)	25.9 (7/27)	0.404
Immuno-suppressive drugs	Tacrolimus	48.6 (18/37)	30.0 (3/10)	55.6 (15/27)	0.269
	Everolimus	32.4 (12/37)	60.0 (6/10)	22.2 (6/27)	0.049
	MMF	67.6 (25/37)	70.0 (7/10)	66.7 (18/27)	>0.99
	Cyclosporine	24.3 (9/37)	30.0 (3/10)	22.2 (6/27)	0.679
	Corticosteroids	16.2 (6/37)	10.0 (1/10)	18.5 (5/27)	>0.99
COVID-19 symptoms	Cough	51.5 (17/33)	62.5 (5/8)	48.0 (12/25)	0.688
	Dyspnea	24.2 (8/33)	50.0 (4/8)	16.0 (4/25)	0.074
	Fever	60.6 (20/33)	87.5 (7/8)	52.0 (13/25)	0.108
	Gastrointestinal	30.3 (10/33)	75.0 (6/8)	16.0 (4/25)	0.005
	Myalgia	42.4 (14/33)	25.0 (2/8)	48.0 (12/25)	0.416
COVID-19 management	IST interruption or modification	57.6 (19/33)	87.5 (7/8)	48.0 (12/25)	0.098
	Antibiotics	48.5 (16/33)	100.0 (8/8)	32.0 (8/25)	<0.001
	Corticosteroids	18.2 (6/33)	37.5 (3/8)	12.0 (3/25)	0.137
	Remdesivir	23.5 (8/34)	88.9 (8/9)	0.0 (0/25)	<0.001
	Supplemental O_2	16.2 (6/37)	60.0 (6/10)	0.0 (0/27)	<0.001
	Incubation	0.0 (0/37)	0.0 (0/10)	0.0 (0/27)	
	Death	5.4 (2/37)	20.0 (2/10)	0.0 (0/27)	0.068

LT, liver transplantation; HTN, hypertension; DMII, diabetes mellitus type II; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis; AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; IST, immunosuppressive therapy

requiring therapeutic drug monitoring [93]. Non-hospitalized LT patients who are receiving calcineurin or mTOR inhibitors should be administered either an anti-SARS-CoV-2 mAb or remdesivir as first-line therapy [94]. Recent data suggest that the administration of remdesivir for 3 days reduces the risk of hospitalization/death by 87% [95]. Ritonavir-boosted nirmatrelvir may be given with caution. The reintroduction or dose adjustment of calcineurin and mTOR inhibitors in patients who have completed therapy with ritonavir-boosted nirmatrelvir should be guided by therapeutic drug monitoring, as shown in Table 3. Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, and "Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir" [51].

As mentioned above, observational studies have shown that immunosuppressive therapy containing tacrolimus is associated with better survival in LT patients infected with SARS-CoV-2 [82]. On the other hand, mycophenolate is an independent factor for severe COVID-19 [83]. Lowering immunosuppression, primarily antimetabolites, in LT recipients with active SARS-CoV-2 infection has not been shown to increase the risk of rejection, as long as liver biochemistries are regularly monitored [73,78,96]. AST recommends holding MMF with active COVID-19 infection for 5-10 days, or until symptoms resolve, and then restarting as tolerated. Lowering the dosage or stopping immunosuppressants without monitoring liver biochemistries may cause a flare, especially in patients with autoimmune hepatitis (AIH), or precipitate acute rejection [97]. Some studies indicated that, after adjustment for multiple risk factors, LT recipients may not be at significantly greater risk of death compared to the general population with COVID-19 [8,73,75,76,78].

Table 3 Special precautions when using RBN in LT patients receiving CNI or mTOR inhibitor

Drug	When to start RBN	Drug monitoring
Envarsus	48 h from last dose	Day 3-7 after last day of RBN
Tacrolimus	24 h from last dose	Day 3-7 after last day of RBN
Cyclosporine	24 h from last dose	Day 3-7 after last day of RBN
Everolimus	48 h from last dose	Day 3-7 after last day of RBN
Sirolimus	48 h from last dose	Day 3-7 after last day of RBN

RBN, ritonavir-boosted nirmatrelvir; LT, liver-transplanted; CNI, calcineurin inhibitors; mTOR, mammalian target of rapamycin

The optimal management strategies for COVID-19 in immunocompromised hospitalized patients are not clearly defined. Clinical experience suggests that LT patients have the expected responses to recommended therapies for COVID-19 [51,92,98]. SARS-CoV-2 is most infectious during the onset of symptoms, but infectivity decreases after approximately 10 days in mild-to-moderately ill patients and 20 days in severe-to-critically ill and immunocompromised patients [99]. Immunocompromised patients with COVID-19 who do not require supplemental oxygen during hospitalization are recommended to receive remdesivir for 5-10 days, given the risk of prolonged viral replication. Dexamethasone should be added if the immunocompromised patient has escalating oxygen requirements (high-flow nasal cannula, noninvasive ventilation, or mechanical ventilation) [98]. Therapeutic anticoagulation for LT patients hospitalized for COVID-19 should be managed similarly to anticoagulation for other hospitalized patients [51,98].

Adding interleukin (IL)-6 inhibitors and Janus kinase (JAK) inhibitors to dexamethasone improves clinical outcomes in patients with severe COVID-19 [92,98]. However, dexamethasone is a moderate inducer of CYP3A4, and IL-6

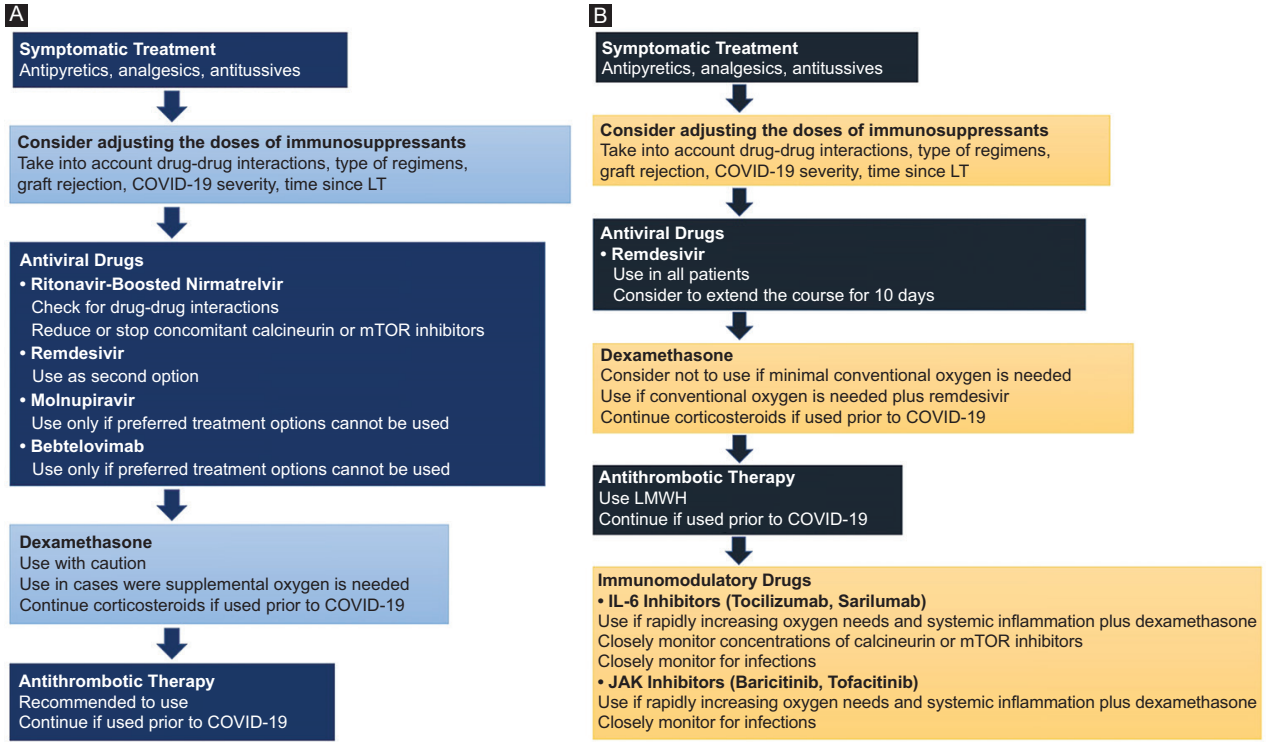

Figure 3 (A) Treatment guidance for non-hospitalized LT patients with COVID-19, (B) treatment guidance for hospitalized LT patients with COVID-19

LT, liver transplantation; mTOR, mammalian target of rapamycin; LMWH, low molecular weight heparin; IL-6, interleukin-6; JAK, Janus kinase

inhibitors may lead to increased metabolism of CYP substrates. Clinicians should closely monitor the serum concentrations of calcineurin and mTOR inhibitors when these drugs are used [51]. Immunosuppressed patients who receive both corticosteroids and tocilizumab or baricitinib may be at increased risk for both routine and opportunistic infections and careful monitoring is required. There is insufficient data regarding the use of COVID-19 convalescent plasma (CCP) in hospitalized or non-hospitalized immunocompromised patients [51,92].

In the absence of evidence, some clinicians would consider using additional treatments in hospitalized patients who are immunocompromised with severe symptoms attributed to viral replication, despite the use of other therapies (such as remdesivir), because humoral immune responses may be reduced or absent in this population. Treatments such as anti-SARS-CoV-2 mAbs (under Emergency Investigational New Drug provisions, if available) that have activity against dominant circulating variants, or high-titer CCP collected from vaccinated donors who were infected with SARS-CoV-2 within the past 6 months, can be used [51,92]. Comprehensive guidance for the management of COVID-19 in non-hospitalized and hospitalized LT patients is summarized in Fig. 3A,B.

Concluding remarks

LT programs around the world have been deeply affected by the outbreak of the COVID-19 pandemic. Most LT centers reduced their transplant activity because of inadequate resources and the increased risk of nosocomial spread, factors that were considered to outweigh the benefit of performing an LT. Additionally, professional associations of hepatology and transplant providers recommended that LT should be limited to emergency cases and that each center should evaluate any operation on a case-by-case basis, giving priority to patients with acute liver failure or ACLF with high MELD scores, as well as HCC patients at the upper limits of the Milan criteria. Another important issue that was raised during the COVID-19 pandemic is the increased alcohol consumption, and the relapse in abstinent patients, that were both noticed in several countries around the world. LT programs were heavily impacted by this phenomenon, as it resulted in higher MELD scores, increased mortality and a greater frequency of ALC cases in the LT waiting lists. As novel treatment and vaccination strategies against SARS-CoV-2 started to appear, clinicians and researchers tried to incorporate all the new information into their practice. In particular, regarding high-risk groups such as immunocompromised LT patients, it is mandatory that their management should be guided by the latest guidelines, which we summarize in this review. Based on the knowledge that was collected during the COVID-19 pandemic, medical societies should be properly prepared in the future in order to manage similar outbreaks in a more efficient way and with a lower impact on everyday hospital care, including SOT programs.

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