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COVID-19 in liver transplant patients: Impact and considerations.

COVID-19 in liver transplant patients

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Abstract

The Coronavirus disease 2019 (COVID-19) pandemic has significantly impacted liver transplantation worldwide, leading to major effects on the transplant process, including pre-transplant, peri-operative, and post-transplant periods. It is believed that patients with chronic liver disease, especially those with cirrhosis, have a higher risk of complications from COVID-19 infection compared to the general population. However, data evaluating COVID-19 effects on liver transplant patients has not uniformly demonstrated worse outcomes. Nonetheless, the pandemic created significant challenges and restrictions on transplant policies and organ allocation.

Key Words: COVID-19; liver transplantation; immunosuppression; living donor; mortality

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Core Tip: The COVID-19 pandemic exerted significant challenges to the liver transplant structure worldwide, initially resulting in a decline in liver transplants but soon after rebounded. A better understanding of this infection together with robust guidance by the international transplant societies helped offset this decline. A multitude of considerations should be exercised throughout the liver transplant process to maintain acceptable safety and outcomes.

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic was declared an emergency by the World Health Organization (WHO) in March 2020.[1] Since then, it has made major impacts on many aspects of healthcare, including liver transplant in the United States. It greatly affected the pre-transplant, peri-operative, and post-transplant periods of liver transplantation.

It is widely accepted that patients with chronic liver disease, specifically those with cirrhosis, have a higher rate of hospitalization, hospital length of stay, morbidity, and mortality from COVID-19 infection compared to the general population.[2] In a large meta-analysis that included 40 studies mainly from the United States and China with more than 900,000 participants, COVID-19 patients with chronic liver disease had higher odds of developing a severe infection (pooled OR = 2.44; 95%CI, 1.89–3.16) and mortality (pooled OR = 2.35; 95%CI, 1.85–3.00) when compared to COVID-19 patients without chronic liver disease.[3]

In contrast, literature evaluating COVID-19 effects on liver transplant recipients did not consistently demonstrate worse outcomes.[4,5] **A systematic review of 1,522 LT recipients who were infected with COVID-19 did not find a difference in cumulative incidence in morality compared to patients who were not LT recipients. Additionally, the review did not find a difference in mortality between non-LT recipients *vs* LT recipients in patients who received a LT within one year *vs* one-year post-transplant.**[6] Still, the COVID-19 pandemic added significant challenges and restrictions to transplant policies and organ allocation. The healthcare structure was overwhelmed by critically ill patients with COVID-19 resulting in diversion of medical resources away from liver transplantation.[7] Furthermore, early concerns of patients contracting severe COVID-19 infection in light of immunosuppression discouraged their use. These uncertainties culminated in initial hardships in the overall management of patients with chronic liver disease thereby negatively affecting liver transplantation.

To revive the liver transplant process and provide organs for those in dire need, significant changes in liver transplant practice have been implemented per major transplant societies' recommendations. [8]After an initial drop in the number of liver transplants performed in the United States in early 2020, a quick recovery in the latter half of 2020 and early 2021 followed.[9] This was likely due to better understanding of

this disease, improved adherence to infection prevention recommendations and replenished health care resources. Later, COVID-19 vaccination emerged as an efficient and cost-effective preventive strategy for patients with chronic liver disease, further helping to offset COVID-19-related shortcomings. [10]

Discussion:

This comprehensive review discusses the major aspects and effects the pandemic had on the liver transplant process as a whole.

COVID-19 infection in patients with cirrhosis

Pathogenesis

The liver is prone to direct COVID-19 infection because of expressed angiotensin-converting enzyme 2 (ACE2) receptor in the hepatobiliary epithelial cells. Although not fully understood, it is hypothesized that binding of the virus spike protein to ACE2 receptors allows viral entry and subsequent host cellular damage.[11,12] Indirect hepatotoxicity may occur due to hemodynamic instability, drug-induced liver damage, COVID-19-induced immune dysfunction, coagulopathy, and intestinal dysbiosis.[13] Moreover, **since** the ACE2 receptors are also expressed on cholangiocytes, some suggest that COVID-19 infection may worsen cholestasis in patients with primary biliary cholangitis and primary sclerosing cholangitis. [14]

Clinical presentation

Similar to patients without underlying liver disease, patients with cirrhosis typically develop mildly elevated aminotransferase levels (<5 times the upper limit of normal [ULN]); nevertheless, severe acute hepatitis **and** even acute liver failure have also been reported. [15] Commonly, a pattern of AST greater than ALT elevation is associated with disease severity. [16]Likewise, low albumin level is linked to worse COVID-19 disease

severity. It is unknown if this is just a marker of disease severity or merely a risk factor for severe disease.

In patients with cirrhosis, COVID-19 infection may result in hepatic decompensation, similar to other infections. In a retrospective, multicenter study from 13 Asian countries, 29% of COVID-19 patients with chronic liver disease presented with hepatic decompensation. [17]

Histopathological findings

Liver biopsy in patients with COVID-19-induced liver injury is nonspecific. Histopathological changes include microvesicular steatosis, portal and lobular activity, and zone 3 focal necrosis. [18,19] In an autopsy-based series that included 48 cases, liver histologic findings included variable degrees of parenchymal lymphocytic infiltration in almost all patients and hepatic vascular alterations in some cases.[20] In our opinion, performing a liver biopsy does not add diagnostic benefit unless an alternative diagnosis is considered.

Clinical outcomes

A significant body of research suggests increased mortality in COVID-19 patients with chronic liver disease. According to a multicenter, observational from the United States, in those with COVID-19 infection, the presence of cirrhosis was associated with higher mortality when compared to those without cirrhosis (RR 4.6, 95%CI 2.6-8.3).[21] In a database study of COVID-19 patients with chronic liver disease, after adjusting for relevant confounders, the presence of cirrhosis was associated with higher 30-day mortality compared to those without cirrhosis (8.9% vs. 1.7 %; 95%CI 2.91-3.77). [22]A subsequent cohort study found that COVID-19-related mortality increases with cirrhosis progression; patients with Child-Pugh (CP) class B or C cirrhosis were found to have increased mortality (OR 4.90, CI 1.16-20.61 and OR 28.07, CI 4.42-178.46,

respectively). Mortality was mostly attributed to pulmonary complications (79%), whereas liver-related mortality was seen in 12% of patients.[23]

A rare but important long-term sequela of severe COVID-19 is cholangiopathy, at times resulting in progressive biliary destruction and liver failure requiring liver transplantation. [24] In a retrospective study by Faruqui *et al* for patients hospitalized for severe COVID-19, 12 patients ultimately developed some degree of cholangiopathy defined by evidence of cholestasis (Alkaline phosphatase ≥ 3 ULN) or radiologic biliary abnormalities. The majority were male (92%) with a mean time of cholangiopathy diagnosis of 118 days from COVID-19. One patient underwent liver transplantation. [25]

Management

COVID-19 management in patients with cirrhosis follows the same supportive routine measures for the general population, including the use of COVID-specific drug therapy. Deranged liver biochemistries are not an absolute contraindication to using therapy such as remdesivir. **Remdesivir use alone can cause** a further elevation in liver enzymes (up to 10 times the baseline). [26] However, its use is discouraged if the ALT ≥5 ULN.[27] Although Paxlovid (combination nirmatrelvir and ritonavir) trials did not show any concerns about its use in cirrhotic patients, it is extensively metabolized by liver cytochrome P450 enzymes. Thus, this drug harbors the risk of accumulation and toxicity in patients with decompensated cirrhosis. We think this medication should be used judicially and in collaboration with infectious disease specialists.

The use of COVID-19 monoclonal antibodies is encouraged early in the infection course in cirrhosis. This is particularly important because cirrhotic patients tend to mount suboptimal humoral responses to COVID-19 vaccination and **thus** probably also infection. Other used immunomodulatory therapies in treating COVID-19 include JAK inhibitors (baricitinib) and IL-6 receptor antagonists (tocilizumab). [28]We learned from

baricitinib use in rheumatological disorders that it may cause liver biochemistry abnormalities and hence caution and regular monitoring should be exercised. [29] Additionally, the risk of hepatitis B virus reactivation has been documented with both baricitinib and tocilizumab; therefore, obtaining hepatitis B serology before treatment initiation is warranted to assess the need for prophylactic nucleoside analogue therapy.[30]

Prevention

Adherence to general preventive measures to avoid COVID-19 in patients with cirrhosis is paramount. These include social distancing, hand hygiene, proper use of personal protective equipment, and telemedicine clinic visits.[31] It is strongly recommended for patients with cirrhosis to receive the COVID-19 vaccine. [32]In a prospective, multi-center study aimed at comparing the humoral response to the COVID-19 vaccine between patients with chronic liver disease (437 individuals) and healthy controls (144 individuals), chronic liver disease was associated with lower rates of post-vaccination COVID-19 antibody positivity (77% vs. 90%; P = .008). The rate of antibody positivity was similar among patients with chronic liver disease regardless of cirrhosis presence or even decompensation (P = .894).[32] These findings suggest additional doses of COVID-19 vaccine might be warranted in this high-risk patient population to achieve adequate immunity.[33] In a propensity score-matched cohort study of United States veterans with cirrhosis, receiving only one dose of COVID-19 vaccine (either Pfizer BNT162b2 mRNA or a Moderna mRNA-1273) resulted in 64.8% reduction in COVID-19 infection and 100% prevention of hospitalization or mortality due to COVID-19 infection after 28 days. [34]

Pre-transplant impact and considerations

Effect on liver transplant volume

The United States performs the most liver transplants worldwide per year. The second-leading country in the number of liver transplants performed is China, followed closely by Brazil. [35] Currently, over 9,000 Liver transplants are being done every year in the United States. For the past nine years, the number of annual liver transplants has increased steadily, setting annual records.[36] Despite the challenges of the COVID-19 pandemic, the year 2020 was no different, as we witnessed an increase of 10.1% in deceased donor liver transplantation (DDLT). The major impact the pandemic had was on living donor liver transplants (LDLT), which suffered a significant decline of 22% between February and April 2020. The liver transplant performed in the United States between 2018-2021 is depicted in Figure 1.

During the height of the pandemic, non-urgent liver transplantation was deferred to conserve hospital resources. Since the Centers for Medicare and Medicaid services have classified organ transplantation as a tier 3b activity, liver transplant centers were urged to continue the process similarly to before the pandemic.[38] However, patients had to wait longer for their liver transplants during the pandemic, especially for living donor liver transplants. There is data suggesting that patients who were wait-listed for other solid organ transplantation, such as kidney transplant patients, had worse outcomes with a higher risk of hospitalization and death compared to patients who got the transplant sooner. [39]Data on liver transplant patients is lacking in this regard. The COVID-19 effects on liver transplant-listed patients are highlighted in a special online report by UNOS. (Figure 2)

On the other hand, the recent changes in the organ allocation system helped offset some of COVID-19 challenges. As a replacement for geographic areas, nautical miles are now utilized. Priority for receiving organs is triaged by medical urgency within a concentric circle radius of 150, 250 then 500 nautical miles (NM). While this new policy is imperfect as it serves better well-occupied areas in the center of the United States

when compared to other coastal areas, it indeed improved access to solid organs across the country.[41]

COVID-19 positive liver transplant donors and candidates

The American Society of Transplantation (AST) guidelines and Organ Procurement and Transplantation Network (OPTN) formulated guidelines on using COVID-19 positive donors. The consensus early in the pandemic was to avoid liver transplants in active donor-positive situations due to the risk of developing acute respiratory distress syndrome or COVID-19-related thrombosis. However, given the high prevalence of the virus in the community, some transplant centers started transplanting patients with donor positivity in emergent situations.

In one Italian study, seventeen liver transplant patients were studied for more than one year from their transplant with a COVID-19 positive donation, of these one tested positive for 21 days after transplantation however none experienced severe complications from COVID-19. [42]Of note, post-transplant immunosuppression was not adjusted and there was no use of anti- COVID-19 therapy after the transplant. It is important to mention that this study is limited by the small sample size but provided hope for patients receiving a liver transplant from COVID-19 positive donors.

Concern regarding the blood-borne transmission of COVID-19 during liver transplantation discouraged living donor liver transplants initially during the pandemic. However, studies showed that, unlike lung transplant recipients, the risk of transmitting donor-derived COVID-19 infection was not likely in liver transplant patients.[43] Blood-borne transmission does not pose much risk as the degree of COVID-19 viremia is low. [44]

Current literature also suggests a higher risk of contracting COVID-19 infection among healthcare providers compared to the general population.[45] Organ donation from a COVID-19 positive patient also has the risk of exposing all transplant team health professionals who typically work closely with other high-risk cirrhotic patients. On the occasion of transmitted COVID-19 infection to medical staff, self-isolation will exert further strain on healthcare staffing and resources. It is therefore imperative to assess the risks and benefits of using organs from a potentially COVID-19 infected donor.

Liver transplant centers across the nation have developed their protocols and policies to manage listed patients having COVID-19 infection.[46] This is to ensure maximum benefits for their patients, yet as important, cause no harm. In our center, for example, listed patients who get COVID-19 infection get temporarily inactivated until they are symptom-free, and 3 wk have elapsed since their diagnosis. **Moreover, we often perform a contrast-enhanced computed tomography of the chest and pulmonary function tests, if the patient had respiratory symptoms, prior to reactivation. On the contrary, if the patient did not develop any respiratory symptoms, they are reactivated without any further testing.**

Ethical considerations

Fair allocation of liver grafts, possibly the scarcest organ of all, remains an ethical question in those with active COVID-19 infection. [47]The main principle of allocation is to achieve the greatest good for both the patient and the community. While benefiting those needing livers is likely to result in improved survival and health of patients and grafts, a real risk exists in those with active COVID-19 infection of increased mortality or significant surgical complications. Considering the uncertainty regarding outcomes of liver transplant in candidates with active COVID-19 infection, these vital organs are better redirected to more suitable candidates with a higher chance of benefit pending infection resolution. [48]

Additionally, it is important to note that exposure of health care providers to infected transplant patients continues to significantly burden hospital structures throughout the country. The ethical principles of justice and utility should dictate the just allocation of organs to those who would get the greatest benefit.[49]

Post-transplant impact considerations

Risk in liver transplant recipients

The post-transplant risk of COVID-19 is the risk of acquiring severe infection as a solid organ recipient on chronic immunosuppression with an inherent risk of prolonged viral shedding. The Spanish Society of Liver Transplantation (SETH) found that liver transplant recipients may have double the risk of acquiring COVID-19 within an epidemic scenario (standardized incidence ratio: 191.2; 95% CI 190.3-192.2) as compared to age and gender-matched cohort. [50]A 2022 prospective double-center study from southern Italy followed thirty LT recipients who were infected with COVID-19 and found that LT recipients were more often symptomatic but did not have an increased risk for hospitalization or mortality.[51]

Clinical presentation and outcomes

The clinical presentation reported in observational studies included fever (61.4%), cough (58.6%), and dyspnea (36.2%). [52]Webb *et al* reported that gastrointestinal symptoms were common (27.9%). Interestingly, the liver transplant recipients had more gastrointestinal symptoms compared to the control group (30% vs. 12%, p < 0.0001), whereas no significant difference was observed in respiratory symptoms. [53] The same study compared outcomes of COVID-19 infection between those who underwent liver transplant (124 patients) and matched cohorts (474 patients). No difference in hospitalization (82% vs. 76%; P=.106) or need for intensive care unit (31% vs. 30%, P=.837). Twenty-eight (19%) patients in the liver transplant cohort died, compared to 167 (27%) in the matched cohort (P=.046).

In a meta-analysis and systematic review by Kulkarni *et al* [54]which included eighteen studies with a total of 1,522 COVID-19 infected liver transplant recipients, there was no difference in mortality (17·4%) between liver transplant and non-liver transplant COVID-19 patients up to one year post-transplant. Approximately 23% of LT patients had severe COVID-19 infection. Regarding immunosuppression, 71% and 49% of patients were on tacrolimus and mycophenolate mofetil, respectively. More than half of these patients required some adjustment of their immunosuppression. This analysis suggests that COVID-19 infected liver transplant recipients are not at increased risk of poor outcomes.

Management

The severity of COVID-19 infection often dictates the management of immunosuppressive agents. For example, those with a mild disease not requiring oxygen therapy may be managed as an outpatient without adjustment in **their immunosuppressive agents**. In contrast, liver recipient patients with moderate **to** severe COVID-19 infection are often managed in the hospital. Guidance to manage these patients stems largely from expert opinions. It is generally advised to lower the cumulative degree of immunosuppression, particularly **of** mycophenolate. While steroid dose generally requires no modification during an active infection, calcineurin inhibitors drug monitoring is recommended to avoid acute kidney injury.

Other agents used in treating COVID-19 infection include oral antivirals such as molnupiravir and Paxlovid. The former is likely safe and effective in liver recipient patients and considered a drug of choice by many hepatologists.[55] Paxlovid strongly interacts with calcineurin and Mammalian target of rapamicyn inhibitors, so concomitant use is prohibited.[56] In a single-center, retrospective study that included

liver and kidney transplant recipients, COVID-19 monoclonal antibody (casirivimab-imdevimab or bamlanivimab) reduced hospitalization from 32% to 15% (P = 0.045) with no mortality (13% *vs* 0%, P = 0.04).[57]

The Food and Drug Administration issued an Emergency Use Authorization (EUA) in January of 2022 for Evusheld (tixagevimab and cilgavimab), a long-acting monoclonal antibody for pre-exposure prophylaxis of COVID-19 in with moderate to severe immune suppression including those who received a solid organ transplant.[58] This is an appealing preventive option for high risk liver transplant recipients.

It is important to note that the quality of the literature presented in this review was affected by the evolving understanding of the COVID-19 virus, and the ensuing rapid changes in liver society guidelines in response. Moreover, most of the discussed studies were limited by small sample size and retrospective, single-center design affecting the generalizability of their outcomes. In addition, the changes in liver allocation policies that occurred midway through the pandemic may have confounded the overall number of liver transplants performed in the US.

CONCLUSION

Conclusion

While COVID-19 infection appears to be poorly tolerated in patients with chronic liver disease, liver transplant recipients, despite immunosuppression, have a similar rate of complications and mortality when compared to the general population. It is imperative to recognize important drug-drug interactions in liver transplant patients; notably, Paxlovid interaction with calcineurin inhibitors to avoid drug toxicity. We also advocate for wider utilization of monoclonal antibody pre-exposure prophylaxis of COVID-19 infection in liver transplant patients.

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