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

Effect of Pre-Transplant Covid-19 Exposure on Post-Liver Transplant Clinical Outcomes

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ABSTRACT

Background. COVID-19 has led to an unprecedented global health crisis. This situation caused an immediate reduction in solid organ transplantation activity. This study aimed to present the follow-up results of patients with chronic liver disease who underwent liver transplantation (LT) after a history of COVID-19 infection.

Methods. Sociodemographic characteristics and clinicopathological data of 474 patients who underwent LT at Inonu University Liver Transplant Institute between March 11, 2020 and March 17, 2022 were prospectively recorded and analyzed retrospectively. Among these, the data of 35 patients with chronic liver disease who were found to be exposed to COVID-19 infection in the pre-LT period were analyzed for this study.

Results. The median body mass index, Child score, and Model for end-stage liver disease/Pediatric end-stage liver disease scores of the 35 patients were calculated as 25.1 kg/m^2 (IQR: 7.4), 9 points (IQR: 4), and 16 points (IQR: 10), respectively. Graft rejection occurred in 4 patients at a median of 25 days post-transplant. Five patients underwent retransplantation at a median of 25 days post-transplant. The most common cause of retransplantation is early hepatic artery thrombosis. There were 5 deaths during postoperative follow-up. Mortality developed in 5 (14.3%) patients exposed to COVID-19 infection in the pretransplant period, whereas mortality occurred in 56 (12.8%) patients not exposed to COVID-19 infection. There was no statistically significant difference in mortality between the groups ($P = .79$).

Conclusions. The results of this study showed that exposure to COVID-19 before LT does not affect post-transplant patients and graft survival.

COVID-19 has claimed over 6.4 million lives worldwide as of August 15, 2022. This has led to an unprecedented global health crisis [1,2]. The clinical features of COVID-19 may range from asymptomatic, mild symptoms, or severe pneumonia and multiple organ dysfunction syndromes. Multiple risk factors for severe COVID-19 infection include old age, obesity, cardiovascular disease, chronic kidney disease, chronic pulmonary disease, and chronic liver disease (CLD). Chronic liver disease has been shown to be an important risk factor for complications and mortality associated with COVID-19 infection. Although a specific reason behind this has not been shown yet, excessive proinflammatory cytokine release from the liver is thought to play an important role [3]. In addition, it is thought that COVID-19 causes rapid decompensation in liver functions in patients with CLD and that the resulting COVID-19-related hepatocyte damage contributes to mortality and morbidity [4]. Studies also indicated that the patient's immune status might be

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associated with the severity of COVID-19. Infection by COVID-19 usually occurs after the host immune response induction, which contributes to viral control in most infected.

As the COVID-19 infection became more widespread throughout the world, there was an immediate reduction in solid organ transplant activity. Initial reports from some parts of Europe revealed a 25% decline in deceased donation, but at the pandemic's peak, there was a 50% to 90% reduction in deceased organ donation. Similar changes were noticed in the United States, as a review of data from the United Network of Organ Sharing revealed a 35.9% decrease in organ transplantation during COVID-19 [5−7]. The decline in organ donation was driven by a decrease in available intensive care unit beds for maintaining deceased donors and a decreased willingness to use donors with circulatory deaths because postoperative transplant recovery is usually prolonged for recipients of such organs [7−9].

The community infection of COVID-19 is ongoing, but transplantation activities have resumed fully in most countries. Currently, guidelines are implemented that guide these transplants and ensure the protection of both donor and recipient from COVID-19 infection [5,7,9,10]. In a previous publication, we initially shared our experience with COVID-19 infection among staff, donors, and recipients of liver transplantation (LT) [11]. This study aims to present the follow-up results of patients with CLD who underwent LT after a history of COVID-19 infection.

MATERIAL AND METHODS

Type, Place, and Time of Research

The Ministry of Health announced the first officially detected case of COVID-19 in Turkey on March 11, 2020. Sociodemographic characteristics and clinicopathological data of 474 patients who underwent LT at the Inonu University Liver Transplant Institute between March 11, 2020 and March 17, 2022 were prospectively recorded and analyzed retrospectively. Among these, the data of 35 patients with CLD exposed to COVID-19 infection in the pre-LT period were retrospectively analyzed for this study. Four of 35 patients had died before this study was scheduled. Therefore, only the demographic and clinicopathological data of these patients registered in the hospital data processing system were analyzed. In addition to the above-mentioned data of the remaining 31 patients, long-term follow-up results and data on COVID-19 vaccine applications were also recorded. The short-term results of 12 patients who underwent LT after contracting the COVID-19 infection in the first 9 months of the pandemic were presented in our previous study [11]. The data of the 12 patients mentioned were also included in this study.

Study Protocol and Ethics Committee Approval

This observational retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Inonu University Institutional Review Board reviewed and approved this study for noninterventional clinical research (Approval No:2022/2904). Strengthening the reporting of observational studies in epidemiology guidelines was used to assess the likelihood of bias and overall quality for this study [12].

Diagnostic Approaches for COVID-19

The LT patients who applied to our Institute for a routine visit and/or any reason were questioned and evaluated regarding COVID-19 disease or suspected contact. After evaluation of history and physical examination, the patients suspected of COVID-19 were managed according to guidelines prepared by the Scientific Board of the Turkish Republic Ministry of Health [13]. Reverse-transcription polymerase chain reaction (RT-PCR) test was performed on the suspected cases' nasopharyngeal and oropharyngeal swab samples. Thoracic computerized tomography was examined in patients with negative RT-PCR tests and suspected COVID-19 pneumonia, as well as in patients RT-PCR positive with pneumonia. In patients with persistent clinical suspicion but negative PCR, the test was repeated 24 to 48 hours after the previous test. The patients diagnosed with COVID-19 were admitted to the clinics or intensive care units reserved for patients with COVID-19. These patients were evaluated by multidisciplinary team according to national guidelines.

Demographic Features and Data Collection

The questionnaire form, in which demographic and clinical characteristics were questioned, consisted of 46 questions. One of these questions included 22 biochemical blood parameters measured at the time the diagnosis of COVID-19 was confirmed.

The following parameters have been recorded: age, sex, body mass index (kg/m^2), blood group, marital status, occupation, education level, presence of chronic disease (diabetes mellitus, hypertension, asthma, chronic obstructive pulmonary disease, and cardiovascular disease), smoking, LT type (living donor liver transplant and deceased donor liver transplant), retransplantation status, underlying causes (hepatitis B virus, hepatitis C virus, hepatocellular carcinoma, cryptogenic, etc), Child score, Model for end-stage liver disease/Pediatric end-stage liver disease scores, presence of ascites, type of liver graft (right, left, or left lateral), graft weight, graft to recipient weight ratio, cold ischemia times (min), warm ischemia times (min), operation time (min), graft rejection, post-transplant immunosuppressive agents (steroid, tacrolimus, everolimus, and mycophenolate mofetil), status of COVID-19 drug use, hospital stay due to COVID-19 (service and intensive care), vaccination against COVID-19 (Sinovac, Biontec, both, or none), vaccine dose (1, 2, 3, and 4 doses), exposure to COVID-19 after vaccination, hesitancy against COVID-19 vaccines, opinion about the protective effect of the COVID-19 vaccine, opinion on legally mandating the COVID-19 vaccine, sign and symptoms about COVID-19 infection, and biochemical parameters.

Statistical Analysis

IBM SPSS Statistics (IBM SPSS, Inc, Armonk, NY, United States) software version 25.0 was used for statistical analysis. Quantitative data were given as median, 95% CI for median, and IQR values. Qualitative variables were given as numbers and percentages.

RESULTS

Demographic and Clinical Features

Demographic and clinical data of 35 LT patients (men: 23 and women: 12) with a median age of 50 years (95% CI 43-54)

were retrospectively analyzed. The median body mass index, Child, and Model for end-stage liver disease/Pediatric end-stage liver disease scores of the patients were calculated as 25.1 kg/m^2 (95% CI 22.1-27.2), 9 points (95% CI 9-11), and 16 points (95%CI 14-23), respectively. All patients underwent LDLT for primary LT. Twenty-seven patients (77.0%) received a right lobe liver graft, 4 (11.4%) received a left lobe graft, and 4 (11.4%) received a left lobe lateral segment graft. The median values of graft-to-recipient weight ratio and implanted liver grafts were calculated as 1.01 (95 %CI 0.96-1.28) and 755 g (95% CI 690-780), respectively. The median operation time was 510 minutes (95% CI 480-540), ranging from 270 to 1215 minutes. The median cold and warm ischemia times were 93 minutes (95% CI 80-118) and 55 minutes (95% CI 52-63), respectively.

Graft rejection occurred in 4 patients (11.4 %) at a median of 25 days after LT. Three were acute, and one was a chronic rejection; the patient who developed chronic rejection was retransplanted. Five patients (14.3%) underwent retransplantation (3 LDLT and 2 DDLT) at a median of 25 days after LT. The causes of retransplantation were early hepatic artery thrombosis (n = 4) and late chronic rejection (n = 1). Patients were followed for a median of 574 days (95% CI 454-637) after LT. Five (14.3%) of these patients died within a median of 23 days after LT. Causes of mortality were cardiac problems (n = 4) and complications associated with mesenteric ischemia (n = 1). None of the mortality was secondary to complications associated with COVID-19 infection. The recipients' demographic, clinical, and operative characteristics were summarized in Table 1.

Table 1. Demographic, Clinical, and Operative Characteristics of Recipients

Parameters	Results
Age (y)	50 (43-54)
Sex (m/f]	23 (65.7%)/12 (34.3%)
BMI (kg/m^2)	25.1 (22.1-27.2)
MELD Score	16 (14-23)
Child Score	9 (9-11)
GRWR	1.01 (0.96-1.28)
Graft Weight (g)	755 (690-780)
CIT (min)	93 (80-118)
WIT (min)	55 (52-63)
Operation time (min)	510 (480-540)
Follow-up (d)	574 (454-637)
Liver graft type (Right/Left/Left lateral)	27 (77)/4 (11.4)/4 (11.4)
Pretransplant ascites (Presence/Absence)	21 (60)/14 (40)
Post-transplant rejection (Yes/No) (%)	4 (11.4)/31 (88.6)
Retransplantation (Yes/No) (%)	5 (14.3)/30(85.7)
Etiology (%)	
HBV	7 (20.0)
Cryptogenic	9 (25.7)
HBV+HCC	3 (8.57)
BCS	3 (8.57)
BCS+HCC	1 (2.85)
HBV+HDV+HCC	1 (2.85)
Cryptogenic (acute on chronic)	2 (5.71)
Caroli	1 (2.85)
HCC	2 (5.71)
Wilson Disease	1 (2.85)
Hepatoblastoma	1 (2.85)
PBC	1 (2.85)
Autoimmune	1 (2.85)
Cryptogenic+HCC	1 (2.85)
Biliary Atresia (Kasai procedure)	1 (2.85)
Outcome	
Alive	30 (85.7)
Dead	5 (14.3)

Quantitative variables are given as the median (95% CI), Qualitative variables are given as numbers (%).

BCS, Budd-Chiari syndrome; GRWR, graft to recipient weight ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; PBC, primary biliary cholangitis.

COVID-19–related Features

Patients included in the study underwent LT after a median of 37 days (95% CI 26-54) after diagnosis of COVID-19 infection. Whereas 32 patients stated that they had not been vaccinated against COVID-19 before COVID-19 infection, 3 patients stated that they were vaccinated a median of 206 days (min-max: 152-237) before COVID-19 exposure. Fourteen (40.0%) patients stated they had a median of 2 COVID-19 vaccines (IQR: 1; min-max: 1-4) after LT. Only 1 pediatric patient was found to have COVID-19 disease 238 days after LT. This patient survived the disease process without any problems.

Five of the patients had diabetes mellitus only, and 2 had both diabetes mellitus and coronary artery disease. Six patients with diabetes mellitus used insulin for blood sugar regulation, and one used an oral antidiabetic agent. None of the patients had a serious lung disease requiring medication, but 4 said they smoked.

A positive PCR test confirmed the diagnosis of COVID-19 in 33 patients, and the PCR test was negative in 2 patients. Still, the clinical and thorax computed tomography (CT) findings were considered positive because symptoms were compatible with COVID-19. Thorax CT findings were also positive in 7 of 33 patients with positive PCR, and thorax CT findings in 13 patients were negative. Thorax CT was not required in the remaining 13 patients because lung symptoms did not develop.

The clinical features varied from patient to patient; however, the most common symptoms were fever (n = 14), loss of appetite (n = 13), cough (n = 9), dyspnea (n = 5), headache (n = 10), low back pain (n = 6), fatigue (n = 20), myalgia (n = 10), loss of taste (n = 9), and loss of smell (n = 10). It was learned that 8 patients were hospitalized due to the severity of the symptoms, and one was intubated in the intensive care unit. Although drug treatment was recommended to all patients according to the treatment protocol recommended by the Ministry of Health, it was determined that only 15 patients agreed to receive antiviral treatment.

Opinions from 26 patients were obtained regarding vaccine applications. Fifteen (57.7%) of these patients stated that they had no hesitation against the COVID-19 vaccine, 15 (57.7%) of them thought it was protective, and 14 (53.8%) believed it should be made mandatory by law. COVID-19–related characteristics and patients' opinions about vaccination were summarized in Table 2.

Table 2. COVID-19-related Characteristics

Parameters	Results
From COVID-19 to LT (d)	37 (26-54)
Vaccination before COVID-19 exposure (%)	
Yes	3 (8.6)
No	32 (91.4)
Vaccination after COVID-19 exposure (%)	
Yes	14 (40.0)
No	21 (60.0)
Comorbidity requiring treatment (%)	
DM	5 (14.3)
DM + coronary artery disease	2 (5.7)
Diagnostic tools for COVID-19 infection	
PCR (positive) + thorax CT (no-required)	13
PCR (positive) + thorax CT (positive)	7
PCR (positive) + thorax CT (negative)	13
PCR (negative)+ thorax CT (positive)	2
Clinical symptoms	
Fatigue	20 (57.1)
Fever	14 (40.0)
Loss of appetite	13 (37.1)
Myalgia	10 (28.6)
Headache	10 (28.6)
Loss of smell	10 (28.6)
Loss of taste	9 (25.7)
Cough	9 (25.7)
Back pain	6 (17.1)
Dyspnea	5 (14.3)
Antiviral treatment use (%)	
Accepted	15 (42.9)
Refused	20 (57.1)
Opinions about the COVID-19 vaccine	
No hesitation against the COVID-19 vaccine (n = 26)	15 (57.7)
I believe the vaccine is protective (n = 26)	15 (57.7)
Vaccination should be made mandatory by law (n = 26)	14 (53.8)

CT, computed tomography; DM, diabetes mellitus; LT, liver transplantation; PCR, polymerase chain reaction.

Comparison of Patients With and Without Pretransplant COVID-19 Exposure

During this study period, a total of 474 patients underwent LT. Whereas 35 of these patients were exposed to COVID-19 infection in the pretransplant period, 439 had no exposure to COVID-19. Mortality developed in 5 (14.3%) patients exposed to COVID-19 infection in the pretransplant period, whereas mortality occurred in 56 (12.8%) patients not exposed to COVID-19 infection. There was no statistically significant difference in mortality between the groups ($P = .79$). That is, pretransplant exposure to COVID-19 is not associated with posttransplant mortality.

DISCUSSION

As the COVID-19 pandemic subsides, the global health care community struggles to recover and adapt to the major changes the disease forces. These changes include reductions in inpatient services, losing some patients to follow-up, and increased daycare services and telemedicine use. The loss of follow-up precipitated by the pandemic has resulted in many patients not receiving much-needed care, especially in cancer care and care for patients with end-organ diseases [1,2,5,10].

The pandemic also significantly affected the delivery and access to solid organ transplantation worldwide. Solid organ transplantation greatly benefits patients with end-stage organ disease, providing longer survival and better quality of life. Despite this urgent need of many patients, there was a significant reduction in solid organ transplantation during the pandemic. The reduction in solid organ transplantation is multifactorial. One of the factors implicated is the fact that there was a decrease in deceased organ donation during the COVID-19 pandemic. Another factor is the reduced waitlist registration and increased waitlist suspension. Finally, there is also increased waitlist mortality [7,14−17].

There is fear that LT and the immunosuppression that follows may result in the reactivation of COVID-19 infection and its long-term complications, but studies have not documented this. There are recommendations to allow at least 2 weeks for complete recovery from COVID-19 before LT, but there have been reports of solid organ transplants in patients with active COVID-19 infection. Our study's median time from recovery to LT was 37 days, ranging from 7 to 272 days. In a case reported by Gao et al [18], they reported a case of a 4-year-old who was transplanted for hepatoblastoma 3 days after recovery from COVID-19 with no disease reactivation. There were other cases reported by heal et al [19], Martini et al [20], and Manzia et al [21]. They reported cases of LT after recovery from COVID-19. The time from recovery to LT was 4, 9, and 9 days, respectively. A systematic review by Nacif et al [10] found that the median interval from recovery to LT was 19 days.

Though the case fatality of COVID-19 is low, long-term sequela that may interfere with the quality of life has been reported in up to 80% of patients who suffered from COVID-19. One of the long-term effects reported in post−COVID-19 infection is dyspnea experienced by these patients because of post−COVID-19 lung disease, characterized by residual pulmonary fibrosis with consequent reduction of pulmonary diffusion capacity. They also experienced myocarditis and cardiac arrhythmias. These sequelae in a patient with background liver disease may worsen the patient's condition and result in waitlist suspension. The sequelae may also affect the outcome of the LT procedure and immediate post-transplant outcome due to the changes in the cardiopulmonary system [15,17,22,23].

Infection by COVID-19 is also associated with a coagulation abnormality, which may result in an increased risk for thrombus formation. These changes are precipitated by COVID-19 −induced platelet dysfunction and the production of immature platelets during COVID-19. These changes can last for 10 days after recovery from COVID-19 because of the half-life of platelets. So, patients who received LT within 10 days of COVID-19 infection may be at risk of thrombosis of the hepatic artery, portal vein, and hepatic veins, all of which will result in graft failure [23−26]. In our study, 4 cases of hepatic artery thrombosis resulted in graft failure with the need for retransplantation. In a case series reported by Kulkarni et al [27], they performed LT for 6 patients who recovered from COVID-19. In their series,

none of the patients developed hepatic artery thrombosis. The interval between recoveries from COVID-19 to LT in their study was at least 15 days, and by this time, the COVID-19 −induced platelets dysfunction is expected to have recovered. Another reason for the lack of hepatic arterial complications in their series is that all patients are adults. In contrast, 4 patients are younger than 12 years in our study.

The post-transplant mortality rate in our study is 14.3% (5 patients), and none of the deaths were COVID-19 related. In addition, there was no statistical difference in post-transplant mortality between patients with and without COVID-19 exposure during this study period. The series by Kulkarni et al [27] reported an early mortality rate of 20%, and the mortality is from sepsis, not COVID-19 related. These results show that LTs, which are in the recovery period after exposure to COVID-19 and performed approximately 3 weeks later, do not affect patient survival. However, these results need to be supported by different studies.

Some studies have postulated that COVID-19 infection in solid organ transplant recipients places them at a higher risk of rejection [15,28]. However, there is currently no study on the effect of previous COVID-19 infection on graft rejection after LT. In our study, we had 3 cases of acute rejection occurring within a median of 25 days, and they were treated with an escalation of immunosuppression. There is one case of chronic rejection that required retransplantation.

This study has some limitations. First, this study has a retrospective design. Because standard protocols were not applied to all patients in such studies, it is difficult to comment on the implications of the results. In addition, there is always a risk of bias in retrospective studies. Second, the fact that a multicentric study was not designed, which is an ideal approach to increase the sample size and minimize the impact of the centers, is an important limiting factor, but it is very difficult to organize a multicentric study during the pandemic period.

CONCLUSIONS

Even though chronic organ diseases are among the most important risk factors for mortality and morbidity in COVID-19 patients, this study showed that exposure to COVID-19 before LT does not affect post-transplant patients and graft survival.

DISCLOSURES

All the authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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