Coronavirus Precautions: Experience of High Volume Liver Transplant Institute

Adil Başkıran[1], Sami Akbulut[1], Tevfik Tolga Şahin[1], Adem Tunçer[2], Kuntay Kaplan[2], Yasar Bayındır[3], Sezai Yılmaz[1]

[1]Department of Surgery and Liver Transplant Institute, İnönü University Faculty of Medicine, Malatya, Turkey
[2]Department of Surgery, İnönü University Faculty of Medicine, Malatya, Turkey
[3]Department of Infectious Diseases, İnönü University Faculty of Medicine, Malatya, Turkey

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ABSTRACT

Background: *To present the struggle of a high volume liver transplant center against coronavirus infectious disease-2019 pandemic.*

Methods: *Between March 2020 and December 2020, the demographic and clinical data of staff and liver transplant candidates diagnosed with coronavirus infectious disease-2019 in our Liver Transplant Institute were prospectively analyzed.*

Results: *First, 32 healthcare staff were diagnosed with coronavirus infectious disease-2019, and 6 of them were surgeons. Six staff were asymptomatic, while 24 staff had mild or moderate and 2 staff had severe coronavirus infectious disease-2019. All the staff recovered from the disease without any permanent sequela and returned to duty after 2 consecutive negative polymerase chain reaction results within 24-hour intervals. Second, during the preoperative investigation, 6 living liver donor candidates and 13 recipients were tested positive for coronavirus infectious disease-2019 (son = 6, unrelated = 3, cousin = 3, daughter = 2, cadaveric = 1). Eleven patients received favipiravir and 8 did not receive any treatment because they were asymptomatic. Only one recipient who had severe coronavirus infectious disease-2019 died due to multiple organ failure syndrome. One recipient died in the early postoperative period. The median duration from the initial diagnosis of the patients till the transplant procedure was 21 days (min-max: 14-105 days). During the time of operation, the polymerase chain reaction tests of the donors and the recipients were negative, and the thorax tomography images showed no signs of viral pneumonia.*

Conclusion: *Meticulous precautions, multidisciplinary approach, team effort, and organization of facilities can increase the quality of care of these patients in the coronavirus infectious disease-2019 era. Healthcare workers have shown tremendous effort and are the true heroes of this era.*

Keywords: *COVID-19, liver transplantation, living donor liver transplantation, living liver donors, precautions, staff safety*

INTRODUCTION

The coronaviruses have caused 2 large-scale epidemics since the beginning of the 21st century. First one was the SARS-CoV-1 virus which caused the severe acute respiratory syndrome (SARS) observed in Eastern Asia affecting mainly China, South Korea, and Japan between 2002 and 2003. The second smaller scale epidemic affected Saudi Arabia in 2012 and South Korea in 2015 which was caused by MERS-CoV leading to the middle eastern respiratory distress syndrome (MERS).[1,2] The SARS-CoV-2 virus which is responsible for the coronavirus infectious disease-2019 (COVID-19) pandemic has now become a global crisis. First cluster of COVID-19 was seen in December 2019 in Wuhan City of Hubei Province of China and soon spread throughout the world and became a global catastrophe. In January 2020, World Health Organization (WHO) declared the disease as public health emergency of international concern declaring it to be a pandemic.[3]

The diagnostic criteria of COVID-19 include the presence of fever, radiologic evaluation showing inflammatory infiltration and/or leukocytosis/lymphopenia. Confirmation of the case requires either isolation/cultivation of the virus from the samples obtained from the respiratory tract or positive polymerase chain reaction (PCR) showing the viral genome in these samples.[4] The mean incubation period between the viral entry and onset of the symptoms is 5.2 days and can be as long as 12.5 days, and the infected individuals can spread the virus during this period. Currently, the mortality rate is 2%-5%, and there are certain risk groups with higher mortality risk such as the elderly and the patients with comorbidity.

Corresponding author: ***Sami Akbulut****, e-mail:* ***akbulutsami@gmail.com***
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Coronavirus infectious disease-2019 has overwhelmed the healthcare systems around the world. The priorities have changed including the organization of the intensive care units, operation rooms, and emergency departments. The healthcare professionals have given their full attention to patients with COVID-19, and the treatment of other important diseases such as cancer, cardiovascular disease, rheumatologic disorders, and even acute conditions such as appendicitis have been postponed or management protocols have been altered.[5-7] Patients with end-stage liver failure and transplant candidates are a special group of patients who need special attention.[8] In our previous study, we have reviewed the delirious effects of COVID-19 and its impact on patients with liver disease and liver transplant (LT) candidates.[9] In the present study, we have aimed to evaluate the rate of COVID-19 in healthcare personnel in a specialized center for liver transplantation despite the necessary protection measure that has been taken. Furthermore, we have evaluated the outcome of LT following COVID-19 in donor candidates and recipients.

MATERIALS AND METHODS

Organization of the Staff and Facilities and Importance of Screening of the Staff During COVID-19

Before beginning the study, first, approval was obtained from the Ministry of Health, General Directorate of Health Services, Scientific Research Studies Unit. After that, ethical approval was obtained from İnönü University institutional review board for non-interventional studies (2020/1373). Our transplant center, which was actively performing LT since 2002, was re-organized as Liver Transplant Institute in 2016. Annually, we are performing nearly 300 LT. There are 250 healthcare staff and 25 of them are surgeons who are actively involved in LT activities.

Risk Assessment and Triage of Liver Transplant Candidates During COVID-19

In March 2020, as the first case was confirmed in Turkey, Ministry of Health limited all elective operations in all hospitals in the country and in our institute, and we initiated a risk assessment and delayed the operation of the patients who had no significant risk of decompensation or dropout. In addition to this, we started a strict surveillance program in the transplant candidates, donors, and their relatives who would assist them in the in-patient wards. Liver transplantation in adults was performed only if it met the following criteria: (i) transplant candidates with a Model for End-Stage Liver Disease (MELD) score > 19, (ii) candidates with hepatocellular carcinoma (HCC) that have tumors within Milan criteria and tumor diameter > 2 cm (in the first months of the pandemic), (iii) patients with primary sclerosing cholangitis with 3 or more cholangitis attacks within the last 3 months, (iv) patients whose condition worsened in the last 3 months follow-up (10% or more increase in the MELD score during the follow-up period); (v) furthermore, patients with intractable ascites with or without respiratory distress. Liver transplantation in children was performed only if it met the following criteria: (i) children with pediatric end-stage liver disease scores (PELD) score > 11, (ii) children with hepatoblastoma, (iii) children with biliary atresia who have undergone Kasai operation and have had an attack of cholangitis in the prior 2 months, (iv) children with metabolic disease who had 2 or more episodes of decompensation in the last 6 months.

Preoperative Evaluation Protocol for Recipients and Living Liver Donor Candidates During COVID-19 Era

The living liver donors and the recipients are routinely screened for SARS-CoV-2 with reverse transcriptase polymerase chain reaction (RT-PCR) and thorax computerized tomography (CT). A detailed anamnesis is obtained from the donors, recipients, and the family members to determine information regarding travel to high-risk regions/countries or contact with infected people or who have been to a high-risk region/country. A negative RT-PCR result is required 24-48 hours before the LT procedure from both the donor and the recipient. Furthermore, we also perform thorax CT for both the recipient and the donor. If there is a positive result, the procedure is postponed for 21 days, and the screening procedures are repeated. At least 2 consecutive negative PCR results are required before continuing with the transplant procedure. The recipients and the donors are recommended to have influenza and pneumococcal vaccine prior to the procedure, at the latest.

Our workup strategy for donor and recipient preparation has not changed, and it has been reported previously in a study from our institute.[10] However, priority is given to transplant patients (recipients and donors) so that the tests are performed quickly to avoid transmission of SARS-CoV-2 in common facilities that are crowded. Our informed consent has been changed as well and a phrase stating that the patients and their relatives accept the risks of transplantation during COVID-19 era.

Statistical Analyses

All statistical analyses were performed using Statistical Software Package for Social Sciences (SPSS) version 25

(IBM Corp.; Armonk, NY, USA). Continuous variables were expressed as median (range). The categorical variables were expressed as total number or affected individuals and percentage (n, %).

RESULTS

The Healthcare Personnel

Since March 2020, 32 healthcare staff from our institute were diagnosed with COVID-19 and 6 of them were surgeons (18.7%). The diagnoses of the staff were performed as a result of positive PCR tests, filiation studies, and radiologic evaluation in suspected cases with negative PCR results. Six staff were asymptomatic, while 24 staff had mild or moderate COVID-19 and 2 staff had severe COVID-19. All of them received the appropriate treatment according to the guidelines released by the Turkish Ministry of Health.[11] The clinical characteristics of the symptomatic staff included fever (n = 25), cough (n = 17), myalgia (n = 32), anosmia (n = 15), ageusia (n = 15), headache (n = 28), diarrhea (n = 3), and low back pain (n = 12). Median age of the affected individuals was 30 (min-max = 25-41 years), and 15 were female (46.9%) and 17 were male (53.1%). All the staff recovered from the disease without any permanent sequela and returned to duty after 2 consecutive negative PCR results within 24-hour intervals. Earliest duration for the personnel to return to duty was 21 days. Two staff with severe pneumonia were able to return to work 21 days after the diagnosis of the COVID-19 disease.

The epidemiologic studies such as filiation studies are performed with great care in Turkey. The personnel from Ministry of Health contact patients with COVID-19 and potentially exposed individuals who were in contact with the infected individual. The staff were mostly infected after taking care of a donor or recipient candidate who was found to be positive during the screening period. Less commonly, the staff contracted with the virus from an infected relative within the same house such as parents, spouse, or siblings, etc.

COVID-19 Positive Recipients and Living Liver Donor Candidates: Our Experience

Between March 11 (the date of first confirmed COVID-19 patient in Turkey) and December 31, 2020, we performed 197 LT (186 primary living donor liver transplantation (LDLT), 2 primary deceased donor liver transplantations (DDLT), 4 living donor re-transplantations, and 5 deceased donor re-transplantations). We performed our routine surveillance program as we have previously explained, and during this time period, 6 living liver donors and 13 recipients were tested positive for COVID-19 (son = 6, unrelated = 3, cousin = 3, daughter = 2, cadaveric = 1). Eleven patients received favipiravir and 8 did not receive any treatment because they were asymptomatic. The most frequent symptoms in these patients were low back pain, myalgia, and fatigue. Only 1 recipient had severe COVID-19 who was admitted to the intensive care unit, and this patient died due to multiple organ failure syndrome. One recipient was enlisted for DDLT after a negative PCR test because the patient had no suitable donor. One recipient died in the early postoperative period. The median duration from the initial diagnosis of the patients till the transplant procedure was 21 days (min-max: 14-105 days). The procedures that were planned between 14th and 21st days were planned due to decompensation of the recipient who did not respond to appropriate medical therapy. During the time of the operation, the PCR tests of the donors and the recipients were negative and the thorax CT images showed no signs of viral pneumonia. One of these patients who were operated died on the postoperative 5th day due to complications related to the surgical technique that was not related to COVID-19. The demographic and clinical characteristics of 19 patients with COVID-19 are summarized in Table 1.

DISCUSSION

Coronavirus infectious disease-2019 infection is a disease that causes serious mortality and morbidity around the world. Mortality rate is very high, especially in patients with comorbid diseases such as diabetes mellitus, cardiac disease, pulmonary disease, and solid organ transplant patients. Chronic liver disease and LT are among the most discussed topics in the COVID-19. However, the studies on LT candidates have been from centers with very limited experience. One of the reasons for this due to the fact that many transplant programs stopped during the epic rise of the COVID-19 pandemic. Furthermore, especially DDLT came to a halt, as well. In our opinion, it is necessary to keep the balance well in the COVID-19 era. Unfortunately, many patients who do not have an LT face the risk of mortality. Therefore, LT should be performed in patients with high MELD score, refractory ascites, and esophageal variceal bleeding, provided that necessary precautions are taken. Our study is unique for it is the first study to address the outcome of the medical staff and patients in a center of excellence for liver transplantation. Our results have shown that the rate of infection is reduced among both healthcare personnel and the donor candidates and patients if necessary precautions are taken. So far, our protocol has worked very efficiently, and we wanted to share our experiences and protocol with other centers in the field.

Table 1. Demographic and Clinical Characteristics of 19 Patients with Preoperative COVID-19 Positivity

COVID-19 (+) Patients	Sex	Age	BMI	Surgery	Relationship of the Donor to the Recipient	Etiology	Outcome
Recipient	F	44	27.3	DDLT	Cadaveric	PBS	Alive
Donor	M	23	23.7	LDH (right)	Son		Alive
Recipient	F	44	18.7	Right LDLT	Son	Cryptogenic	Alive
Recipient	M	2	16.1	Left lateral	Unrelated	Biliary atresia	Alive
Donor	M	32	26.2	LDH (right)	Cousin		Alive
Donor	F	27	21.8	LDH (right)	Cousin		Alive
Recipient	M	66	28.4	Right LDLT	Son	HBV	Exitus (postop)
Recipient	M	56	28.4	Right LDLT	Son	HBV	Alive
Recipient	F	55	20.9	Left LDLT	Unrelated	Cryptogenic	Alive
Recipient	M	45	27.2	Right LDLT	Cousin	HBV	Alive
Donor	M	34	23.6	LDH (right)	Son		Alive
Recipient	M	60	31.6	Right LDLT	Son	Cryptogenic	Alive
Donor	F	33	24.8	LDH (right)	Daughter		Alive
Donor	M	25	24.2	LDH (right)	Son		Alive
Recipient	M	52	27.4	Right LDLT	Son	HBV	Alive
Recipient	M	54	18.1	Right LDLT	Son	HBV	Alive
Recipient	M	57	22.8	Right LDLT	Daughter	Cryptogenic	Alive
Recipient	M	48	26.1	No surgery	No surgery	Hemochromatosis	Exitus (preop)
Recipient	F	1	17.8	Left lateral	Unrelated	Biliary atresia	Alive

COVID-19, coronavirus infectious disease 2019; DDLT, deceased donor liver transplantation; LDH, living donor hepatectomy; PBS, primary biliary cirrhosis.

The protection of healthcare staff has the at most importance and is vital for the continuation of the healthcare service. However, healthcare professionals are in the front line and are at increased risk of contracting the disease, and therefore, every measure should be taken to protect the healthcare staff.[12] The American Association for the Study of Liver Diseases (AASLD) has stated that each transplant center is responsible for the decision-making process for transplant candidates during the pandemic. They have suggested that transplantation is a procedure that cannot be postponed. However, AASLD predicted that the number of organ donations would fall and that centers would have to perform risk stratification, giving priority to candidates with high MELD score, patients with a high decompensation risk, and patients with tumor because of the risk of progression during the period on the waiting list. Therefore, each center was advised to regularly check its own facilities such as the intensive care unit beds together with the ventilators, availability of the operating room together with the staff, and availability of blood products, all of which have a significant impact on the transplant procedures.[13] The recommendations of the Center for Disease Control and WHO should regularly be checked for any update in the management protocol for special patient groups. Currently, there are no data regarding blood-borne transmission of COVID-19, and transplantation from a COVID-19-positive donor is not recommended. Therefore, routine surveillance of the donors, transplant candidates, and their relatives as well as the healthcare professionals is recommended.[14] Nevertheless, all the guidelines that are currently available are related with DDLT. The data related with LDLT are not enough. Therefore, there is a need for definitive guidelines to help the centers that mainly perform LDLT. There are 36 intensive care beds and 114 single-bed rooms in in-patient wards in our institute. In addition, 80% of the transplantations that are performed in our institute are LDLT. Therefore, if we share our experience regarding the precautions that are being performed in our institute, this would guide other centers that mainly perform LDLT.

The risk factors for prolonged viral shedding include male gender, presence of any comorbidities, individuals with a

severe form of the disease and systemic corticosteroid therapy and initiation of Lopinavir/ritonavir in the first week following the diagnosis of the disease.[14] Furthermore, there are few case reports that show transplant recipients with uneventful infection period but prolonged viral shedding up to 2 months.[15,16] Therefore, transplant recipients with COVID-19 are also a public health problem because they can spread the virus and infect other individuals if left undetected.

The current guidelines suggest a strict surveillance program for both the recipient and the donor before the procedure. Nevertheless, the transplant procedures should be prioritized to patients with high MELD scores and patients with HCC due to the risk of waiting list dropout.[17-19] The surveillance procedure includes thorax CT and RT-PCR testing of the respiratory tract samples of the recipient and the donors. In the deceased donors, lower respiratory secretions can also be tested, although it is not routine for liver but exclusive for lung transplantations.[20,21] We have performed a strict surveillance program to detect the asymptomatic individuals, and we have delayed the transplant procedure whenever it is necessary. American Society of Transplantation[20] suggests that if the living donor is known to have COVID-19, then the procedure should be postponed until negative test results are obtained. Furthermore, in donors with a high-risk contact history, the procedure should be postponed for at least 14 days, and a routine nucleic acid test with RT-PCR and thorax CT should be obtained. The transplant procedure can only be performed if the following criteria are met: (i) the interval between the diagnosis and the procedure is between 21 and 90 days (regardless of the result of the last RT-PCR), (ii) a negative test is obtained after appropriate treatment, and (iii) strict adherence to the recommendations of the local infectious disease control committee. We postpone the operation for 21 days in cases for whom either the recipient or the living liver donor has a positive RT-PCR test. We require 2 consecutive negative RT-PCR test results in 24 hours to proceed with the transplantation which is performed 21 days after the initial diagnosis of COVID-19.

The host protein that mediates the attachment and entry of SARS-Cov-2 is the angiotensin-converting enzyme-2 (ACE-2) receptor. It is expressed in majority of the cells in the body and in the respiratory tract, it is expressed in the type II alveolar cells, and the bronchial epithelial cells express very weak ACE-2.[22,23] In the skin, it is expressed in the basal layer of the epidermis, eccrine glands, and the myocytes of the subcutaneous vasculature and those surrounding the sebaceous glands. In the brain, only endothelia of the dural sinuses and the smooth muscle cells are positive for ACE-2. Remarkably, ACE-2 is expressed by the endothelium of nearly all vessels. Furthermore, ACE-2 expression is observed in cholangiocytes, cardiomyocytes, and membrane of adipocytes, but it is not observed in the endothelium of the liver sinusoids, hepatocytes, and the Kupfer cells.[23,24] It is abundantly present in the digestive tract including the enterocytes in the small intestine and the components of the upper gastrointestinal tract with the exception of the enterocytes of the colon.

The immunopathology of interaction of SARS-CoV-2 and the human host is very complex. However, it is now known that there are some events that take place as SARS-CoV-2 infects the humans. First of all, the virus can infect lymphocytes which causes a loss of function and depletion. In addition to this, the activated innate immune system that releases vast amount of proinflammatory cytokines to the systemic circulation leads to cytokine storm which activates certain pathways such as programmed cell death protein-1 (PD1), T cell immunoglobulin domain and mucin domain-3 (TIM3), and killer cell lectin-like receptor subfamily C member 1 (NKG2A) which leads to lymphocyte exhaustion.[25] A massive proinflammatory stimulus leads to immune paresis (exhaustion of the immune system) which causes a relatively immunosuppressed state that increases the tendency for secondary microbial infections. It has been shown that in fungal antigen (1,3)-β-D-glucan levels were prominently elevated in individuals with severe COVID-19 who have lymphopenia.[25] In addition, Chen et al[26] have shown that positive polymicrobial culture results are obtained from patients with severe COVID-19. A pending immune paresis/immunosuppression that increases the risk of infection causes a potent exacerbation in the inflammatory cascade that results in cytokine production which results in inflammation and causes end-organ damage in lungs, liver, kidneys, and the heart. Therefore, infiltrations in the lung and disorders of gas exchange, high transaminases, urea and creatinine, creatine kinase, and lactate dehydrogenase are common findings in cases with severe COVID-19.[26-29]

Whether SARS-CoV-2 can cause a direct injury to liver because of the viral replication cycle is not known. The ACE-2 receptor is expressed in the cholangiocytes which suggests that the portal triad is the site of viral replication. However, only the transaminases have been reported to be elevated in individuals with severe form of the disease (but not in mild to moderate disease) and the cholestatic have been reported to be in the normal range.[30] This suggests

that the cytokine storm and the antiviral treatment are the main mechanisms underlying acute liver injury observed in severe COVID-19.[9,31] However, there are reports of acute decompensation of individuals with chronic liver disease with high mortality rates reaching 60% in patients with Child B and C cirrhosis.[20] Furthermore, Gurala et al[32] have reported an 80-year-old male without pre-existing liver disease who developed acute liver failure 4 days after the initial diagnosis of COVID-19. If the deceased donor has a positive test for SARS-CoV-2, the transplant procedure should not be performed.

There have been several different observations regarding COVID-19 in the recipients in the posttransplant setting. In the beginning of the pandemic, D'Antiga et al[33] have reported that they had only 3 cases of COVID-19 among a large cohort of 700 pediatric liver diseases and no mortality was observed. Bhoori et al[34] have analyzed 111 previously and 40 recently operated transplant recipients and stated that they had 3 patients in each group that had COVID-19. They stated that only the patient with COVID-19 in the previously operated group showed mortality. Similarly, Huang et al[35] have reported 59-year-old male patients transplanted in 2017 for Hepatitis B virus (HBV) and HCC who had chronic rejection and died due to severe COVID-19. Qin et al[15] reported prolonged viral shedding reaching 2 months in a 37-year-old LT recipient.

These studies suggest that LT recipients do not have a higher risk for mortality due to COVID-19. However, the risk of severe COVID-19 increases with increasing graft dysfunction. Another point that needs emphasis is the prolonged viral shedding (carrier state) in these patients because of the immunosuppression which is a major public health risk. In the literature, there are 11 studies investigating the factors that may influence the mortality in LT recipient.[36-46] Colmenero et al[43] have reported that the incidence of severe COVID-19 doubled when compared to non-transplanted population, and also mycophenolate mofetil doses exceeding 1000 mg increased the risk of mortality in these patients. Merli et al[44] have also found that mycophenolate mofetil doses exceeding 1000 mg increased the risk of mortality. Rodriguez-Peralvarez et al[39] also suggested that calcineurin inhibitors can be continued, but antimetabolites affected the prognosis of COVID-19 adversely. Other studies did not report any risk factor for immunosuppressive treatment regimens.[36-38,40-42,45,46]

Whether a modification of immunosuppressive regimen is required in transplant recipients is a matter of debate. It has been suggested by various societies to keep the current immunosuppressive treatment in mild to moderate disease. However, in severe COVID-19, it is usually recommended to discontinue antimetabolites such as mycophenolate mofetil and to taper or discontinue calcineurin inhibitors. In this case, steroids with a daily dose of 10 mg is stated to prevent rejection and also to prevent progression of COVID-19 severity.[17-19]

CONCLUSION

Since the beginning of the pandemic in Turkey in March 2020, the healthcare system has been overwhelmed by the surge of the cases; however, our dedicated team has shown tremendous effort, and we have developed our own guidelines for protection and management of our cases, organized our facilities, and we continued to perform LT with thorough risk assessment. The healthcare personnel were screened regularly. Due to our efforts, only 1 recipient (0.5%) died among the 197 new LT that we have performed between March and December 2020. These are the days of crisis; extreme measures are necessary both to treat the patients with COVID-19 and also to continue the management of patients with other critical illnesses. Patients with end-stage liver disease are a very susceptible patient group that requires continuous attention. Multidisciplinary approach, team effort, and organization of facilities can increase the quality of care of these patients in the COVID-19 era. Healthcare workers have shown tremendous effort and are the true heroes of this era.

Ethics Committee Approval: Ethics committee approval was received for the study from the İnönü University Institutional Review Board for Non-interventional Studies (2020/1373).

Informed Consent: Since this study was prepared as a retrospective data analysis, informed consent was not obtained from the patients for this study.

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