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Effect of COVID-19 Pandemic on Patients Who Have Undergone Liver Transplantation Because of Hepatocellular Carcinoma

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ABSTRACT

Background and Aim. Many clinical studies have shown that the COVID-19 case fatality rate is higher in older patients, those with comorbidities, those with immunosuppressive conditions, and those who stay in the intensive care unit. This study aims to evaluate the clinical outcomes of 66 liver transplant (LT) patients with primary liver cancer who were exposed to COVID-19 infection.

Methods. Demographic and clinical data of 66 patients with primary liver cancer (hepatocellular carcinoma = 64, hepatoblastoma = 1, cholangiocarcinoma = 1) who underwent LT in our institute and were exposed to COVID-19 infection between March 2020 and November 2021 were analyzed in this cross-sectional study. The following data of the patients were recorded: age, sex, body mass index (kg/m^2), blood group, underlying primary liver disease, smoking, tumor characteristics, post-transplant immunosuppressive agents, COVID-19 symptoms, hospitalization, intensive care unit stay, intubation, and other clinical features.

Results. There were 55 (83.3%) male and 11 (16.7%) female patients, with a median age of 58 years. Sixty-four patients were exposed to COVID-19 only once, whereas the remaining 2 patients were exposed 2 and 4 times, respectively. After exposure to COVID-19, it was determined that 37 patients used antiviral drugs, 25 were hospitalized, 9 were followed in the intensive care unit, and 3 were intubated. One intubated patient was under hospital follow-up because of biliary complications before exposure to COVID-19, and this patient died from sepsis.

Conclusion. The low mortality rate of LT patients with primary liver cancer exposed to COVID-19 infection can be attributed to background immunosuppression that prevents cytokine storm. However, it is appropriate to support this study with multicenter studies to make strong comments on this issue.

THE first case of severe acute respiratory syndrome coronavirus 2 was detected in China in December 2019 [1,2]. The disease was very contagious and spread rapidly worldwide, so the World Health Organization declared a global pandemic in March 2020 [2]. The infection was widespread and contagious, occurring at different times in different parts of the world. It also occurred in different waves caused by different virus variants [2,3].

The case fatality rate of COVID-19 has been reported as 10.0%, but the case fatality rate mainly regards older patients, those with comorbidities, those with immunosuppressive conditions, and those who stay in the intensive care unit (ICU) [4]. Risk factors that predict mortality in COVID infection include age >50 years, obesity, diabetes, and malignancy. Other factors

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include acute kidney injury and elevation of inflammatory markers [5−7]. The clinical features of COVID-19 are subject to variation and may range from asymptomatic infection to pneumonia, cytokine storm, and death [5−7].

One of the factors associated with mortality in COVID-19 infection is cytokine-mediated inflammation (cytokine storm) [8−11]. The mechanism responsible for cytokine storm is believed to result from an infection of the alveolar epithelium through the angiotensin-converting enzyme-2 receptor. The infection activates the acute inflammatory cascade from activated macrophages, B cells, and T lymphocytes [8−11]. These activated cells are responsible for releasing proinflammatory cytokines, which exacerbates the ongoing inflammatory process. The result of all these processes causes inflammatory exudates and erythrocytes to migrate into the alveoli, resulting in dyspnea, respiratory failure, and death [8−11].

Solid organ transplant recipients are maintained on immunosuppressive medications and may have associated comorbid diseases that put them at high risk of complications from COVID-19. However, the role of immunosuppression on the outcome of COVID-19 infections has been disputed in some studies [8,12,13].

Liver transplantation (LT) is the second most common form of solid organ transplant. Liver transplantation for hepatocellular carcinoma (HCC) accounts for 15% to 50% of all LTs performed. Patients with HCC are already immunocompromised from the malignancy, and after LT, patients are maintained on an immunosuppressive regimen to prevent rejection [14,15]. Based on these assumptions, patients who received LT for HCC are at increased risk of severe COVID-19 infections and poor outcomes because of chronic immunosuppression and high rates of comorbidities. This study aimed to evaluate the clinical outcomes of 66 LT patients with primary liver cancer who had COVID-19 infection.

MATERIALS AND METHODS

Type, Place, and Period of Research

The medical data of all patients who have undergone LT for primary liver cancer (known or incidentally detected) at Inonu University Liver Transplant Institute were evaluated for this cross-sectional study. Between March 11, 2020, when COVID-19 infection was detected in Turkey, and November 1, 2021, 66 patients who had undergone LT because of primary liver cancer (HCC = 64; hepatoblastoma = 1; cholangiocarcinoma = 1) in our institute were exposed to COVID-19 infection. Sixty-five patients who survived after exposure to COVID-19 were contacted by phone and asked questions about clinical data and awareness of COVID-19 infection and the COVID-19 vaccine. Because 1 remaining patient died from COVID-19 infection, only the data from this patient in the hospital's database were used. The time between COVID-19 positivity and the last control or mortality date was evaluated as the follow-up period.

Study Protocol and Ethics Committee Approval

Before starting the study, permission was obtained from the Directorate of Liver Transplant Institute (approval no. 2021/93896), and then ethical approval was obtained from the Inonu University Institutional Review Board for noninterventional clinical research (approval no. 2021/2549). This study involving human participants followed the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Population and Sample Size

In the study period mentioned above, a total of 66 patients who had undergone LT because of primary liver cancer at our Liver Transplant Institute and were confirmed to be COVID-19 positive in the light of polymerase chain reaction, clinical examination, and radiologic findings were determined as the population of this study.

Sociodemographic and Clinical Characteristics

The following data of the patients were recorded: age, sex, body mass index (BMI: kg/m^2), blood group, underlying primary liver disease (hepatitis b virus [HBV], hepatitis c virus [HCV], hepatitis D virus [HDV], autoimmune liver disease, cryptogenic, etc.), smoking, chronic disease (diabetes mellitus, hypertension, asthma, cardiovascular disease), LT type (living donor liver transplantation [LDLT], deceased donor liver transplantation [DDLT]), Child score, Model for End-Stage Liver Disease (MELD) score, tumor characteristics (within or beyond Milan, Malatya, University of California−San Francisco [UCSF], and Barcelona Clinic Liver Cancer [BCLC] criteria), tumor differentiation (well, moderately, poorly), total tumor diameter (cm), tumor number, tumor recurrence, post-transplant immunosuppressive agents (steroid, tacrolimus, everolimus, mycophenolate mofetil), symptoms related to COVID-19, antiviral drug use for COVID-19, hospitalization because of COVID-19 (service, ICU, intubation), COVID-19 vaccination status (Sinovac [Beijing, China], BioNTech [Mainz, Germany], both, none), vaccine dose (1, 2, 3, 4), pre-vaccination COVID-19 exposure, and post-vaccination COVID-19 exposure.

Postoperative Immunosuppressive Protocol

We can summarize our immunosuppressive treatment protocol for HCC: corticosteroid therapy is started intraoperatively, and the dose is gradually reduced and discontinued at the third to sixth month postoperatively. Tacrolimus is started at postoperative days 3 (POD3), and the dose is adjusted to maintain blood levels of 6 to 10 ng/mL for the first year. Mycophenolate mofetil is started at POD3 and discontinued after POD30, taking into account the clinical condition of the HCC patients. Everolimus is started at POD30, and then it is dose adjusted to maintain blood levels of 8 to 10 ng/mL for the first year. After the first year, dose adjustments are made so that tacrolimus and everolimus blood levels are 3 to 5 and 5 to 8 ng/mL, respectively. This protocol can be modified depending on the infection status, presence of autoimmune disease, renal dysfunction, and development of acute or chronic rejection episodes.

Statistical Analysis

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

RESULTS

A total of 66 patients with primary liver cancer, 55 (83.3%) male and 11 (16.7%) female, with a median age of 58 years (95% CI = 56-61), were included in this study. The median BMI and MELD score of the patients were calculated as 26.1 kg/m^2 (95% CI = 25.5-26.9) and 12 (95% CI = 10-14), respectively. Sixty-four patients had HCC (97%), 1 (1.5%) had hepatoblastoma, and the remaining (1.5%) had cholangiocarcinoma. In terms of the underlying disease, the first 4 most common liver diseases were as follows: HBV (n = 38; 57.6%), cryptogenic (n = 9; 13.6%), HBV + HDV (n = 8; 12.1%), and HCV (n = 6; 9.1%). The median total tumor number, total tumor diameter, and pretransplant alpha-fetoprotein levels were calculated as 1 (95% CI = 1-2), 3 cm (95% CI = 2-5), and 6 (ng/mL) (95% CI = 5-20), respectively. Forty-three (67.2%) HCC patients met the Milan criteria, and 48 (75.0%) met the Malatya criteria. Sixty-one (92.4%) HCC patients underwent LDLT, and the remaining 5 (7.6%) underwent DDLT. The patients were followed for a median of 1200 days (IQR = 1505; 95% CI = 944-1587), and only 3 patients developed tumor recurrence during this period. Patients stated that they used 1 or more of the following during COVID-19 exposure: tacrolimus (92.4%), everolimus (66.7%), steroid (10.6%), and mycophenolate mofetil (9.1%). Mycophenolate mofetil treatment was discontinued in all patients, and the dose of tacrolimus was decreased in 5 patients with high blood levels.

Sixty-four patients were exposed to COVID-19 only once, whereas the remaining 2 were exposed 2 and 4 times, respectively. After exposure to COVID-19, it was determined that 37 patients used antiviral drugs, 25 were hospitalized, 9 were followed in the intensive care unit, and 3 were intubated. One intubated patient was under hospital follow-up because of biliary tract complications before exposure to COVID-19, and this patient died from sepsis. Fifty-two patients (78.8%) stated that they were vaccinated against COVID-19. Thirty-eight (73.1%) patients stated they were exposed to COVID-19 before vaccination, and 16 (30.8%) were exposed to COVID-19 after vaccination. Twenty-one patients indicated that they were vaccinated with BioNTech alone, 18 with Sinovac alone, and the remaining 13 patients with both vaccines. The clinical signs and symptoms of the patients were as follows: fatigue (72.7%), fever (63.6%), headache (62.1%), myalgia (62.1%), backache (50.0%), cough (48.5%), dyspnea (34.8%), loss of taste (43.9%), loss of smell (36.4%), and diarrhea (28.8%). Sixty-five patients were followed for a median of 310 days (95% CI = 208-356) after COVID-19 exposure, and no patient developed serious

Table 1. Quantitative variables of 66 LT Patients who were exposed to COVID-19

Variables	Results
Age	
Median (IQR)	58 (13)
95% CI	56- 61
BMI	
Median (IQR)	26.1 (4.6)
95% CI	25.5-26.9
MELD Score	
Median (IQR)	12 (8)
95% CI	10-14
AFP (ng/mL)	
Median (IQR)	6 (51)
95% CI	5-20
Tumor number	
Median (IQR)	1 (1)
95% CI	1-2
Total tumor diameter (cm)	
Median (IQR)	3 (3)
95% CI	2-5
From LT to COVID-19 (d)	
Median (IQR)	918 (1406)
95% CI	726-1496
From COVID-19 to last follow-up (d)	
Median (IQR)	310 (310)
95% CI	208-356
Number of PCR tests	
Median (IQR)	2 (2)
95% CI	2-3
Number of vaccination	
Median (IQR)	3 (1)
95% CI	3-4

AFP, alpha-fetoprotein; BMI, body mass index; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; PCR, polymerase chain reaction.

Table 2. Qualitative Variables (Demographic, Clinical, and Tumor-Related Features) of 66 LT Patients Who Were Exposed to COVID-19

Variables	N	Percentage
Sex (male/female)	55/11	83.3/16.7
Blood group (0/A/B/AB)	22/24/13/7	33.3/36.4/19.7/10.6
Child (A/B/C) (n = 64)	26/29/9	40.6/45.3/14.1
Diabetes mellitus (yes/no)	18/48	27.3/72.7
Hypertension (yes/no)	14/52	21.2/78.8
Pulmonary disease (yes/no)	3/63	4.5/95.5
Etiology		
HBV	38	57.6
Cryptogenic	9	13.6
HBV + HDV	8	12.1
HCV	6	9.1
Cholangiocarcinoma	1	1.5
Hepatoblastoma	1	1.5
HBV + ethanol	1	1.5
Autoimmune hepatitis	1	1.5
Metabolic disease	1	1.5
Milan (within/beyond) (n = 64)	43/21	67.2/32.8
Malatya (within/beyond) (n = 64)	48/16	75.0/25.0
UCSF (within/beyond) (n = 64)	50/14	78.1/21.9
BCLC (within/beyond) (n = 64)	52/12	81.3/18.7
LT type (LDLT/DDLT)	61/5	92.4/7.6
Differentiation (well/moderately/poorly) (n = 64)	32/28/4	50.0/43.8/6.3
Tumor recurrence (yes/no)	3/63	4.5/95.5
Tacrolimus use (yes/no)	61/5	92.4/7.6
Everolimus use (yes/no)	44/22	66.7/33.3
Mycophenolate mofetil use (yes/no)	6/60	9.1/90.9
Corticosteroid use (yes/no)	7/59	10.6/89.4

BCLC, Barcelona Clinic Liver Cancer; DDLT, deceased donor liver transplantation; HBV, hepatitis B virus; HCV, Hepatitis C virus; HDV, hepatitis D virus; LDLT, living donor liver transplantation; UCSF, University of California–San Francisco.

Table 3. COVID-19–Related Features (Clinical Presentation and Vaccination)

Variables	n	Percentage
Vaccine against COVID-19 (yes/no)	52/14	78.8/21.2
Pre-vaccination COVID-19 exposure (yes/no) (n = 52)	38/14	73.1/26.9
Post-vaccination COVID-19 exposure (yes/no) (n = 52)	16/36	30.8/69.2
Type of vaccine (BioNTech/Sinovac/both) (n = 52)	21/18/13	40.4/34.6/25.0
Antiviral use (yes/no)	37/29	56.1/43.9
Hospitalization (yes/no)	25/41	37.9/62.1
ICU stay (yes/no)	9/57	13.6/86.4
Intubation (yes/no)	3/63	4.5/95.5
Clinical features (yes/no)		
Fever	42/24	63.6/36.4
Cough	32/34	48.5/51.5
Dyspnea	23/43	34.8/65.2
Headache	41/25	62.1/37.9
Backache	33/33	50.0/50.0
Diarrhea	19/47	28.8/71.2
Fatique	48/18	72.7/27.3
Myalgia	41/25	62.1/37.9
Loss of taste	29/37	43.9/56.1
Loss of smell	24/42	36.4/63.6

ICU, intensive care unit.

COVID-19–related morbidity. Demographic, clinical, and COVID-19 infection–related characteristics are summarized in Tables 1, 2, and 3, respectively.

DISCUSSION

One of the main components of LT is the need for post-transplant optimal immunosuppressive medication use. This is necessary to reduce rejection, ultimately leading to graft loss [14]. Post-transplant immunosuppression is a double-edged sword because it prevents graft loss and, at the same time, it predisposes recipients to repeated infections [16]. With the appearance of the COVID-19 pandemic, one of the main fears of transplant surgeons and physicians was that post-transplant immunosuppression would predispose recipients of solid organ transplants to COVID infection. However, multiple studies reported that immunosuppression after LT is not associated with an increased risk of COVID infection. Guarino et al [17] found that the incidence of COVID-19 infection among recipients of LT is not more than that of the general population. Bhoori et al [18] and Mocchegiani et al [19] also reported that the incidence of COVID-19 among recipients of LT on immunosuppression is not more than in the general population.

Another consideration in recipients of LT infected with COVID-19 is that the infection is expected to be severe because of the background immunosuppression. There was an assumption that these patients may require more hospital admission, ICU care, and possible intubation. In our study, an admission rate of 37.8% was observed. The ICU admission rate was found to be 13.6%, and the intubation rate was 4.5%. A similar study by Guarino et al [17] reported a hospitalization rate of 16.7%, with an ICU admission rate of 6.6%. They also reported an intubation rate of 6.6%. The hospitalization rates reported by Dumotier et al [20] and Webb et al [21] were also higher than our findings. Their study's hospitalization rate was 67% and 82%, respectively. Webb et al [21] reported ICU admission and intubation rates of 28% and 20%, respectively. The findings from our study are different because we only included patients that had LT for HCC, whereas all the studies cited included all patients that had a transplant.

The overall vaccination rate in our patients was 78.8%, but only 24.2% were vaccinated before COVID-19 infection. This is similar to the studies of Boyarsky et al [22] and Marion et al [23]. Their studies reported a vaccination rate among LT recipients of 20% and 16%, respectively. One of the main hindrances to COVID-19 vaccination among recipients of LT is the hesitancy to accept vaccination among these patients. Hesitancy rates of 3.3% and 14.7% have been reported in studies by Constantino et al [24,25].

The case fatality rate of COVID-19 infection varies. Alimohamadi et al [4] conducted a meta-analysis and found that the overall case fatality rate for COVID-19 was 10.0%. In their analysis, the CFR among hospitalized patients was 13.0%. The case fatality rate rose to 37% in patients admitted to the ICU among patients. The overall case fatality rate among our patients was 1.5%. Among hospitalized patients, the case fatality rate in our study was 4%, whereas the case fatality rate was 11.1% among those admitted to the ICU. The case fatality rate in our study is low compared to the case fatality rate reported in the general population because of the background immunosuppression in our patients that prevents cytokine storms. One of the factors associated with mortality in COVID-19 infection is cytokine-mediated inflammation (cytokine storm) [8–11]. In recipients of LT on immunosuppressive medications, macrophage, B-cell, and T-cell activation is inhibited, which may result in reduced cytokine storms. Reducing cytokine storms is responsible for decreased mortality in recipients of LT with COVID-19 infection [8,12,13].

CONCLUSIONS

In summary, the outcome of patients with COVID-19 infection after LT for primary liver cancer, such as HCC, is relatively good. The good outcome can be attributed to background immunosuppression that prevents cytokine storms. However, we believe that it is appropriate to support this study with multicenter studies to make strong comments on this issue.

DISCLOSURES

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

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.transproceed.2023.01.038.

DATA AVAILABILITY

No data was used for the research described in the article.

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