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Short-term experiences of a liver transplant centre before and after the COVID-19 pandemic

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Abstract

Background/Aim: With the COVID-19 pandemic, managing the process of solid organ transplantation has become a significant matter for transplant centres. In this study, we report our experiences on evaluating the effects of COVID-19 in patients with recent liver transplants.

Materials and Methods: We evaluated patients who received liver transplants during three close consecutive periods of time. For transplants conducted between October 1 and December 31, 2019, January 1 and March 10, 2020 and March 11 and June 22, 2020, the lung tomographies of patients were inspected for radiological signs of viral pneumonia. For patients after March 11, 2020, the hospital's electronic database system was scanned for preoperative and postoperative SARS-CoV-2 testing from Real-time Polymerase Chain Reaction (RT-PCR) of the respiratory tract samples.

Results: A total of 149 patients over the age of 18 who received liver transplants at our centre between October 1, 2019 and June 22, 2020 were evaluated. During this time span, our centre conducted liver transplants on patients from 34 different provinces and also abroad. Within this time period, a total of nine patients had respiratory samples with a positive SARS-CoV-2 RT-PCR test. PCR of respiratory tract samples was performed in 21 (14%) patients to identify the other potential infective agents in the respiratory tracts; Rhinovirus and Influenza A were detected in two and respiratory syncytial virus (RSV) was detected in one patient. During the transplant periods, 99 (67.1%) patients were evaluated with computed tomography (CT). The CT findings of 18 (12%) patients were consistent with viral pneumonia. There was a statistically significant difference between the groups only in terms of air bronchogram findings ($P = .012$).

Conclusion: The clinical status of our short-term liver transplant patients was far better than we originally anticipated, but it remains obvious that the necessary precautions should continue to be taken.

1 | INTRODUCTION

On December 31, 2019, the World Health Organisation's China Office reported pneumonia cases of unknown ethology in the Chinese city of Wuhan in Hubei province. On January 7, 2020, the causative agent was identified as a novel coronavirus (2019 nCoV) that was not previously detected in humans.[1] The virus was subsequently termed as SARS-CoV-2. The infectious disease caused by SARS-CoV-2 (COVID-19) has rapidly spread worldwide and has affected life in an unimaginable way. With the COVID-19 pandemic, managing the process of solid organ transplantation has become a significant matter for transplant centres. Since COVID-19 is a contagious disease, it is important to evaluate the donor and potential recipient during the transplantation process, and follow-up on the recipient, who will be receiving immunosuppressive medication.

The World Health Organisation declared a pandemic on March 11, the same day our country reported its first case.[2,3] Throughout the time span between the pre-pandemic period to the first reported case in both the world and our country, one topic of curiosity was whether transplantation patients had signs of viral pneumonia, and if so, its potential link to COVID-19. On the other hand, with the progression of the pandemic period, recipient and donor candidates who had positive preoperative SARS-CoV-2 Real-time Polymerase Chain Reaction (RT-PCR) provided a guideline for the clinical evaluation and short-term follow-up of transplant patients who had contracted COVID-19.

In this study, we report our experiences on evaluating the effects of COVID-19 in patients with recent liver transplants, and believe that it can contribute to the literature during this ongoing pandemic.

What's known

- It is not clear whether solid organ transplant recipients are at higher risk of undertaking SARS-CoV-2 infection than the general population.
- In liver transplant patients, chronic immunosuppression and frequent contact with the health system support the risk of getting COVID-19.
- Life-saving transplantation should continue to be carried out.
- All recipients and donors candidates should be screened for COVID-19.

What's new

- It is critical that recipients within the pandemic period be followed up and consistently evaluated before and following transplantation.
- The clinics of almost all of our COVID-19 cases, who were short-term liver transplant patients, were mild to moderate.
- During our evaluations, recent LT recipients infected with SARS-CoV-2 continued their immunosuppressive treatments without irregularity.
- Thoracic tomographs of patients who underwent liver transplantation in consecutive recent periods, including before the COVID-19 pandemic announcement, were not different in terms of viral pneumonia findings.

2 | MATERIAL AND METHODS

In this study, we evaluated patients who received liver transplants during three close consecutive periods of time at the Organ Transplant Institute of Turgot Ozal Medical Center, Inonu University, Faculty of Medicine. The three time periods were as follows: October 1, 2019-December 31, 2019 being the pre-pandemic period or period I; January 1, 2020-March 10, 2020 being the temporary period or period II (March 10 being the date that the WHO declared a pandemic and the first reported case in Turkey) and March 11-June being the pandemic period or period III. For patients after March 11, 2020, the hospital's electronic database system was scanned for preoperative and postoperative SARS-CoV-2 testing from RT-PCR of nasopharyngeal smear, oropharyngeal smear and/or bronchoalveolar lavage (BAL) samples; positive cases were noted. Patients positive for COVID-19 were retrospectively evaluated for their treatment and follow-up results from electronic case report forms. Retrospective evaluation of post-transplant SARS-CoV-2 RT-PCR control was conducted for 3 months after the evaluation of the last patient. The immunosuppressive medication that patients are receiving was noted. The immunosuppressive treatment protocol includes corticosteroids, 5-10 mg/d methyl prednisolone in patients with autoimmune hepatitis, tacrolimus for patients with normal kidney functions and mycophenolate mofetil, basiliximab or tacrolimus in patients with abnormal kidney functions. Everolimus was given to patients with renal dysfunction and as a combination therapy to reduce the side effects of calcineurin inhibitors (CNI) such as tacrolimus.

In addition, for transplants conducted in our centre between October 1, 2019 and December 31, 2019 and January 1, 2020 and March 10, 2020, we retrospectively evaluated the viral agents that were detected (through molecular analysis) in the respiratory tract samples of liver recipients. Likewise, the lung tomographies of patients were inspected for radiological signs of viral pneumonia. Findings from all three time periods were evaluated for statistically significant differences.

2.1 | Statistical analysis

The statistical analyses of the data were performed through SPSS (Statistical Package for Social Sciences) for Windows 22.0 software. Data for qualitative variables were presented as number and percentage, and data for quantitative variables, as mean ± SD.

Kruskal-Wallis test was used to compare independent samples. A value of $P < .05$ was accepted as statistically significant.

2.2 | Ethics

The present study was approved by The Inonu University Medical Faculty non-interventional Ethical Committee (approval no: 2020/868) and Republic of Turkey Ministry of Health, Labor Council for Scientific Research (form no: 2020-06-15T22_12_38).

3 | RESULTS

A total of 149 patients over the age of 18 who received liver transplants at our centre between October 1, 2019 and June 22, 2020 were evaluated. The mean age (mean ± SD) of the patients was 51 ± 13.3 years; 89 (59.7%) were male and 60 (40.3%) female. Fifty-nine liver transplants were conducted between October 1, 2019 and January 1, 2020, 30 liver transplants between January 1 and March 11, 2020 and 60 liver transplants between March 11 and June 22, 2020. During this time span, our centre conducted liver transplants on patients from 34 different provinces and also abroad (Syria, Tajikistan, Turkmenistan and Algeria). Table 1 displays the distribution of gender and location for liver transplant recipients within these three time periods.

In our study, the median follow-up time for retrospective evaluation of postoperative SARS-CoV-2 RT-PCR was 173 days. Within this time period, a total of nine patients had respiratory samples with a positive SARS-CoV-2 RT-PCR test, with one patient who tested positive during preoperative control. Table 2 presents some clinical information regarding the patients and the dates that SARS-CoV-2 RT-PCRs were tested positive. One female patient was tested positive during the preoperative period. The patient's liver transplant was conducted after COVID-19 treatment had been completed and three control SARS-CoV-2 RT-PCR testing of respiratory tract samples were negative. The other eight patients were male. In one patient, SARS-CoV-2 RT-PCR was found positive for the second time 100 days after clinical improvement. The patient had received hydroxychloroquine for his initial infection, and was put on favipiravir for the second infection. Three positive patients did not exhibit signs of viral pneumonia on lung imaging. The other patients exhibited findings such as ground-glass opacities, vascular dilatation, bronchial changes and interlobular septal thickening. None of the patients had required high-flow O_2 or mechanic ventilation support. One patient died during follow-up. The patient died 45 days after diagnosis of COVID-19, and was being monitored for chronic rejection. The patient's cause of death was not associated with COVID-19.

On the topic of organ donors, six (4%) were cadavers. Ninety-seven donors (65%) were male and 52 (35%) were female. The mean age (mean ± SD) for donors was 30.4 ± 8.4. After March 11, 2020, 41 donors (69%) had preoperative SARS-CoV-2 RT-PCR testing; none had a preoperative positive result. In the follow-up, only one male donor had a positive SARS-CoV-2 RT-PCR on the postoperative 5th month.

For post-transplant immunosuppressive medication, 93 (62.4%) recipients received tacrolimus and 51 (34%) received tacrolimus and everolimus.

PCR of respiratory tract samples was performed in 21 (14%) patients to identify potential infective agents in the respiratory tracts; Rhinovirus and Influenza A were detected in two patients in January, and respiratory syncytial virus (RSV) was detected in one patient in March.

During the transplant periods, 99 (67.1%) patients were evaluated with computed tomography (CT). The CT findings of 18 (12%) patients were consistent with viral pneumonia. Table 3 displays the CT findings consistent with viral pneumonia with respect to time period. The patients' thorax CT images were evaluated for ground-glass opacity, consolidation, air bronchogram, crazy paving pattern, septal thickening, vascular dilatation, bronchial changes, pleural effusion and cavitation findings. There was a statistically significant difference between the groups in terms of air bronchogram findings ($P = .012$). The difference was due to patients in the period III. There was no statistical difference with respect to the other findings (Table 4).

4 | DISCUSSION

Management of liver transplant patients before, during and after transplantation is a new challenge considering that transplantation is essential during the ongoing COVID-19 pandemic. Transplant recipients are a population potentially at high risk because of their continuous immunosuppression and higher incidence of comorbidity;

TABLE 1 The distribution of gender and location for liver transplant recipients within the specified time periods

	Gender			Location (Region)		
Time period	M (n), (%)	F (n), (%)	Total	Within the province (n), (%)	Outside the province (n), (%)	Abroad (n), (%)
October 1-December 31 (pre-pandemic period)	36 (61%)	23 (39%)	**59**	5 (9%)	48 (81%)	6 (10%)
January 1-March 10 (temporary period)	19 (63%)	11 (37%)	**30**	2 (7%)	22 (73%)	6 (20%)
March 11-June 22 (pandemic period)	34 (57%)	26 (43%)	**60**	6 (10%)	51 (85%)	3 (5%)
Total	89 (60%)	60 (40%)	**149**	13 (9%)	121 (81%)	15 (10%)

TABLE 2 Some clinical information regarding the patients and the dates that SARS-CoV-2 RT-PCRs were tested positive

P.	Gender/age	Reason for transplant	Time of transplant	Time elapsed between transplant to COVID19 PCR positivity	Lung imaging findings	Treatment	Immunosuppressive Treatment
1	M/47	HBV	October 2019	(2 Times) 229 d after/329 d after	Vascular dilatation/bronchial changes	HQ FAV	TACR-Eve
2	M/51	PSC	February 2020	185 d after	Ground-glass opacity	FAV	TACR
3	M/45	AH	February 2020	179 d after	Fibrotic changes	—	TACR
4	M/35	CR	February 2020	191 d after	Ground glass opacity/ interlobular septal thickening	FAV	TACR-Eve
5	M/57	HBV+ HCC	March 2020	133 d after	Ground-glass opacity	FAV	TACR
6	M/40	HBV	April 2020	139 d after	Ground-glass opacity	FAV	TACR
7	M/64	HBV+ HCC	April 2020	148 d after	Ground-glass opacity	FAV	TACR-Eve
8	M/54	AH	April 2020	144 d after	Parenchymal band and accompanying subsegmental atelectasis	—	TACR-Eve
9	F/43	PBS	June 2020	Detected preoperatively	Parenchymal lower lobe basal fibrotic bands and areas of linear atelectasis	FAV	TACR

Abbreviations: AH, autoimmune hepatitis; CR, chronic rejection; Eve, everolimus; F, female; FAV, favipiravir; HBV, hepatitis B infection; HCC, hepatitis C infection; HQ, hydroxychloroquine; M, male; P, patient; PBS, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; TACR, tacrolimus.

TABLE 3 The distribution of viral pneumonia findings in CT with respect to the time periods

Time period	Probable viral pneumonia cases (n) (%)	Total patients
October 1-December 31 (Period I)	10 (16.9)	59
January 1-March 10 (Period II)	2 (6.6)	30
March 11-June 22 (Period III)	6 (10)	60
Total	18 (12.1)	149

therefore, it will be influential to determine the optimal management of COVID-19 using data from recent transplant patients.

Experiences from previous coronavirus outbreaks suggest that transplant patients have higher sensitivity to infection, higher risk of severe disease and may potentially transmit the infectious virus for a longer period of time.[4] Although similar concerns are expressed for the current pandemic virus, SARS-CoV-2, further studies are required to confirm these effects.[5,6] A study from the United States of America (USA) reported that among 90 solid organ transplant patients diagnosed with SARS-CoV-2, 13 were liver transplant recipients; 30% of the infections had a severe course.[7] Another study from the literature reported that from 200 liver transplant (LT) recipients who applied to their hospital, three were positive for SARS-CoV-2 and none had symptoms associated with pneumonia. However, they also reported that the final status of these three patients remained unknown.[8] Bhoori et al followed up 151 LT patients (111 long-term and 40 short-term recipients). In their study, they reported that three (2.7%) long-term LT patients had died from severe COVID-19 and three (7.5%) short-term LT recipients were positive for SARS-CoV-2, but had survived the disease.[9] In our study, we evaluated 149 adult patients who received a transplant during three different time periods including the pre-pandemic period, temporary period and pandemic period. All of them were in short time period after transplantation (Table 1). The mean time for retrospective evaluation of postoperative SARS-CoV-2 RT-PCR was 173 days (IQR 33). Nine (6%) patients had a positive SARS-CoV-2 RT-PCR of respiratory tract specimen. There are many follow-up cohorts varying in terms of number, duration and the patient group evaluated. In a cohort from the UK involving 4500 participants in a liver transplant facility, the prevalence of COVID-19 was reported to be 0.1%, with n = 5 patients infected. All five cases had a positive SARS-CoV-2 RNA PCR and recovered without requiring aggressive immunosuppressive treatment adjustment.[10] A study from one centre in our country evaluated 683 solid organ transplantation (74 LT recipients) patients (538 outpatient +45 emergency department) and reported that one patient had a positive COVID-19 PCR result, and eight patients had clinical and radiological signs suggestive of COVID-19 disease.[11] The cohort of our centre contains nearly 2000 liver transplant recipients as adults alone. All of the patients included in our study were recent liver transplant recipients who had received their transplant just before or during the pandemic. One female patient exhibited a positive preoperative COVID-19 test. The other patients were diagnosed following the transplantation. Table 2 displays the time elapsed from the transplantation to positive SARS-CoV-2 RNA PCR test. In the literature, some studies reported the duration between transplantation and COVID-19 morbidity to be 5.3 to 9.3 years, while other studies reported short-term cases (two patients diagnosed within 2 months following transplantation).[12-14]

During the time frame specified, liver transplantation was performed in our medical facility for patients coming from 34 different Turkish provinces as well as internationally from Syria, Tajikistan, Turkmenistan and Algeria. (Table 1). Despite an extensive follow-up, one of our Syrian patients passed away as a result of chronic rejection 45 days after being diagnosed with COVID-19 (not associated with the cause of death). A nationwide American study reported that Blacks and Hispanics have the highest mortality rates, which was thought to be because of a lack in "social distancing opportunity." This statement is supported by another study which reported that 29/36 of solid organ transplant recipients were Hispanic.[15]

Of the LT recipients in our study, 93 (62.4%) were using tacrolimus and 51 (34%) were using both tacrolimus and everolimus as post-transplant immunosuppressant drugs. Patients under immunosuppression were thought to be high-risk individuals for COVID-19, but emerging data may suggest the contrary; immunosuppression in LT recipients may not always be risky and could provide a positive effect by regulating the immune host response against COVID- 19.[9] It is critical that recipients within the pandemic period be followed up and consistently evaluated following transplantation. Physicians should also be cautious of lowering immunosuppression doses as it carries the risk of organ rejection. During our evaluations, recent LT recipients infected with SARS-CoV-2 continued their immunosuppressive treatments without irregularity. The literature reported that recent LT recipients (within 2 months) infected with SARS-CoV-2 continued their induction therapy with basiliximab and high-dose methylprednisolone without an increase in any radiological abnormality or serious complication.[14] Liver transplantation specialists in Beijing suggested the continuation of immunosuppressive treatment for patients with mild SARS-CoV-2 infections, while moderate to severe cases should have their calcineurin inhibitor doses reduced.[16] The EASL-ESCMID report emphasises the importance of drug-drug interactions and antiviral treatment protocols while adjusting immunosuppressive drug dosage.[17]

The possibility of clinical deterioration after transplantation for a recipient with an undiagnosed COVID-19 disease proves to be a matter of concern. Lagana et al reported that a 6-month-old baby with biliary atresia developed COVID-19 and severe pneumonia after receiving a LDLT from her COVID-19-positive mother.[18] The transition path in the paper was uncertain. After the 11th of March 2020, 41 (69%) donors had a preoperative control for SARS-CoV-2 RT-PCR, of which 0 were positive in our study. During the follow-up,

TABLE 4 Distribution of lung CT findings within the three time periods and the statistical differences

Imaging finding	Lesion localisation	Time periods			Total (n)	Significance level
		October 1-December 31, 2019 (n)	January 1-March 10, 2020 (n)	March 11-June 22, 2020 (n)		
Ground-glass opacity	Absent	25	19	32	76	0.18
	Unilateral	6	–	3	9	
	Bilateral	6	2	6	14	
	Total	37	21	41	99	
Consolidation	Absent	30	20	35	85	0.39
	Unilateral	6	–	1	7	
	Bilateral	1	1	5	7	
	Total	37	21	41	99	
Air bronchogram	Absent	29	21	40	90	**0.012**
	Unilateral	8	–	1	9	
	Bilateral	–	–	–	–	
	Total	37	21	41	99	
Crazy paving pattern	Absent	35	21	40	96	0.5
	Unilateral	1	–	–	1	
	Bilateral	1	–	1	2	
	Total	37	21	41	99	
Septal thickening	Absent	22	16	27	65	0.74
	Unilateral	4	–	3	6	
	Bilateral	11	5	11	25	
	Total	37	21	41	99	
Vascular dilatation	Absent	31	21	39	91	0.1
	Unilateral	2	–	1	3	
	Bilateral	4	–	1	6	
	Total	37	21	41	99	
Bronchial changes	Absent	31	20	40	91	0.15
	Unilateral	3	1	1	5	
	Bilateral	3	–	–	4	
	Total	37	21	41	99	
Tree-in-bud opacity	Absent	33	20	40	93	0.31
	Unilateral	3	–	0	3	
	Bilateral	1	1	1	3	
	Total	37	21	41	99	
Nodule	Absent	30	19	39	88	0.17
	Unilateral	5	1	–	6	
	Bilateral	2	1	2	5	
	Total	37	21	41	99	
LAP	Absent	37	21	41	99	1.00
	Unilateral	–	–	–	–	
	Bilateral	–	–	–	–	
	Total	37	21	41	99	

(Continues)

TABLE 4 (Continued)

Imaging finding	Lesion localisation	Time periods			Total (n)	Significance level
		October 1-December 31, 2019 (n)	January 1-March 10, 2020 (n)	March 11-June 22, 2020 (n)		
Cavitation	Absent	37	21	41	99	1.00
	Unilateral	—	—	—	—	
	Bilateral	—	—	—	—	
	Total	37	21	41	99	
Pneumothorax	Absent	35	20	41	96	0.33
	Unilateral	2	1	—	3	
	Bilateral	—	—	—	—	
	Total	37	21	41	99	
Pleural effusion	Absent	20	9	24	53	0.45
	Unilateral	6	6	10	22	
	Bilateral	11	6	7	24	
	Total	37	21	41	99	

Note: The significance level is 0.05.

Abbreviations: CT, computed tomography; LAP, lymphadenopathy.

Bold indicates statistically significant.

only a single male donor demonstrated a positive SARS-CoV-2 RT-PCR after the 5th postoperative month. It is highly recommended that both donor and recipient be evaluated for COVID-19 preoperatively,[19] most transplant centres carry this through with a comprehensive history of symptoms and exposure, RT-PCR of an upper respiratory tract sample (eg, nasopharyngeal swab) and chest imaging. Suitable options for evaluation include X-ray imaging as well as thorax/chest CT for patients with respiratory symptoms; candidates with active COVID-19 and/or other respiratory diseases should have their operations delayed. Although the optimal delay time for patients who test positive for an active COVID-19 is not clear, it is highly recommended to wait until all the symptoms have passed and two negative PT-PCR tests for SARS-CoV-2 are given.[20] We delayed the liver transplantation of a 43-year-old female patient found positive preoperatively for SARS-CoV-2 until the completion of her COVID-19 treatment and three negative respiratory RT-PCR tests.

The literature describes the incidence of pneumonia in transplant recipients to be 10.1/1000 per year and reports that 29% are due to viral agents.[21] We evaluated the thoracic computed tomography of 99 (67.1%) patients and our findings suggested that 18 (12%) were compatible with viral pneumonia. Among 10 patients operated between the 1st of October and 31st of December 2019, 16.9% of patients had findings in their thoracic CT that were compatible with viral pneumonia, which leads us to believe that they may have been undiagnosed SARS-CoV-2 patients. 6.6% of the patients operated between the 1st of January and the 10th of March 2020 had findings suggestive of viral pneumonia. The respiratory PCR performed to determine the underlying respiratory agents in 21 (14%) patients showed Rhinovirus and Influenza A as the cause in two patients in January, and RSV as the cause of another patient in March. This situation indicates that as of January, other respiratory viruses began affecting the imaging results. Table 3 shows the distribution of viral pneumonia findings in CT with respect to the time periods. There was a statistically significant difference between the groups in terms of air bronchogram findings ($P = .012$). The difference was due to patients in the third period. There was no statistical difference with respect to the other findings (Table 4). The presence of air bronchogram was not believed to be primarily associated with viral pneumonia. Since the CT evaluations of our patients showed no difference in terms of viral pneumonia findings, we speculated that COVID-19 did not have a negative impact on the transplantation process.

TABLE 5 The number of COVID-19 cases received from the provincial health directorate in our province where our institute is located

Month	Number of tests	Number of positive cases
March	678	63
April	6295	252
May	10 809	105
June	12 918	315

While it has almost been an entire year since the breakout of SARS-CoV-2 (November of 2019),[22] speculations as to when it could end remain uncertain. The period in which our study was conducted included the first period in which the number of daily cases was most common with the onset of the pandemic in our country.[23] 11 April 2020 daily number of cases became 5138.[24] During these periods, the number of COVID-19 cases is shown in Table 5 according to the data we received from the provincial health directorate

in our province where our institute is located. Like the rest of the world, our medical facility must label specific routes that must be taken for solid organ (primarily liver) transplantations. While taking necessary precautions; limiting the number of patients in our polyclinic, providing all of our healthcare and other personnel with protective equipment, limiting the number and duration of patient interactions and through selective operations based on urgency, we provided LT for patients whose conditions were critical.[25] In our study, SARS-CoV-2 RT-PCR test was positive in respiratory samples of 9 of 149 patients who had recently undergone liver transplantation. The clinics of almost all of our COVID-19 cases, who were short-term liver transplant patients, were mild to moderate. One patient, was being monitored for chronic rejection, died 45 days after diagnosis of COVID-19. The patient's cause of death was not associated with COVID-19. Even, mortality rates in liver transplant recipients are reported lower than in the matched general population.[26] On the other hand, as Bhoori et al reported, those with short-time liver recipients may have an advantage over long-term recipients for COVID-19.[9] The clinical status of our LT patients were far better than we originally anticipated, but it remains obvious that the necessary precautions should continue to be taken.

DISCLOSURE

No conflict of interest was declared by the authors. The author declared that this study has not received financial support.

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