



COVID-19 infection frequency and clinical course in patients with liver transplantation: Results of a single transplant center in Türkiye

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ABSTRACT

Objective: In this paper, it was tried to determine the incidence of COVID-19, course of the disease, and mortality rate in liver transplant patients by evaluating all patients operated on in our center. In addition, the results of liver transplantation performed in our center during the pandemic period were also presented.

Material and Methods: All patients who had undergone liver transplantation in our liver transplant center were questioned about their history of COVID-19 either at their routine controls in the clinic or by phone interview.

Results: Our liver transplant unit had 195 registered liver transplantation patients (2002-2020), and 142 of these were still alive and under follow-up. During the pandemic period, 80 patients referred to our outpatient clinic for follow-up, and their records were evaluated retrospectively in January 2021. Among 142 liver transplant patients, a total of 18 (12.6%) COVID-19 patients were identified. While 13 of these patients were males, mean age of the patients at the time of interviews was 48.8 years (22-65 years). Nine of the patients had living donor liver transplant, and the rest had cadaveric liver transplant. The most common COVID-19 associated symptom in the patients was fever. During the pandemic period, 12 liver transplant operations were performed in our center. Nine of them were living donor liver transplantation and the remainder were cadaveric liver transplantations. Two of our patients got COVID-19 positive during this period. One of them who was transplanted after COVID treatment was followed-up in intensive care for a long time and was lost not related to COVID-19.

Conclusion: The incidence of COVID-19 is higher in liver transplant patients than in the general population. Nonetheless, mortality rates are low. During the pandemic period, liver transplantation can be continued by following general precautions.

Keywords: COVID-19 infection, liver transplantation, clinical course

INTRODUCTION

Due to the effects of the pandemic on health system, many elective surgical procedures have been delayed or postponed, and health services associated with coronavirus disease 2019 (COVID-19) have been tried to be sustained. However, patients needing emergent surgery cannot be delayed due to their current vital risks, and oncological surgery patients can not tolerate too much delay due to the risk of progression of their existing diseases. Unlike these, a group of affected surgical patients in the pandemic period was both patients awaiting organ transplantation and those having undergone organ transplantation.

Undoubtedly, liver transplantation has also been affected considerably during the pandemic period. It has been observed that there has been a significant decrease in the number of liver transplantation in many parts of the world since the beginning of the pandemic period (1-3). Serious concerns have arisen among patients awaiting organ transplantation, both about being operated during the pandemic period and the increase in waiting time (4).

Patients with liver transplantation must receive lifelong immunosuppression therapy and therefore live at risk of both communal and opportunistic infections throughout their lives. Although COVID-19 is known to mainly start with fever

Cite this article as: Aydın O, Çolakoğlu MK, Öter V, Özgün YM, Pişkin E, Arı D, et al. COVID-19 infection frequency and clinical course in patients with liver transplantation: Results of a single transplant center in Türkiye. Turk J Surg 2022; 38 (3): 283-288.

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Received: 15.12.2021
Accepted: 19.07.2022
Available Online Date: 19.09.2022

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DOI: 10.47717/turksurg.2022.5612

and respiratory symptoms, it can also occur with many different symptoms. However, there is limited information on how COVID-19 disease onset may occur in patients who have undergone liver transplantation or risk factors and course of the disease due to their current immunosuppressive conditions. While some publications regarding the effects of coronavirus on these patients have reported a mortality rate of up to 30% (5,6), some publications have reported similar mortality rates compared to non-transplant coronavirus-positive patients with similar comorbidities (7). At this point, it is not clear whether immunosuppression is an advantage or a disadvantage in these patients. Some studies provide recommendations for reducing immunosuppression in patients with liver transplantation (8,9). However, the fact that the short-term results in patients receiving immunosuppression are the same as the general population also suggests that immunosuppression may have a protective effect in these patients (10-12). Because of these differences of opinion, transplant centers should monitor their own patients and manage their patients according to these results.

In this paper, it was tried to determine the incidence of COVID-19, course of the disease, and mortality rate in liver transplant patients by evaluating all patients operated on in our center, which is a liver transplant center and provides tertiary health services. In addition, the results of liver transplantation performed in our center during the pandemic period as of March 2020 were also presented.

MATERIAL and METHODS

This study was conducted in January 2021 in gastroenterology surgery clinic. All patients who had undergone liver transplantation in our liver transplant center were questioned about their history of COVID-19 either at their routine controls in the clinic or by phone interview. Information was obtained from them or their relatives regarding whether they had COVID-19 disease or not, their initial symptoms, whether they were hospitalized or not, duration of their treatment, the treatment they received and their ventilator needs. Laboratory results obtained during this period were again obtained from the patients or their relatives. Death information of the patients was obtained from their relatives. Before this interview, patients or their relatives were informed about the study and their verbal consent was obtained. The consent was obtained for the study from the Republic of Türkiye, Ministry of Health. The study was conducted in accordance with good clinical practice principles and the Declaration of Helsinki. Statistical analysis was carried out by a statistician using IBM SPSS Statistics (version 22) software as appropriate.

RESULTS

Ankara City Hospital liver transplant unit had 195 registered liver transplantation patients (2002-2020), and 142 of these patients were still alive and under follow-up. During the pandemic peri-

od (as of March 2020), 80 patients referred to the transplant outpatient clinic for follow-up. COVID-19-related records of these patients were prospectively kept and these records were evaluated retrospectively in January 2021. In addition, COVID-19 related data of the remaining 62 patients were collected by phone call and added to other records during January 2021. Besides, the records of new liver transplant patients who had undergone surgery at our transplant center between March 2020 and January 2021 were also retrospectively evaluated.

Among 142 liver transplant patients, a total of 18 (12.6%) COVID-19 patients were identified through both control examinations and telephone interviews. While 13 of these patients (72.2%) were males, mean age of the patients at the time of the interviews was 48.8 years (22-65 years). Nine of the patients had a living donor liver transplant and the rest had cadaveric liver transplant. While the oldest patient was operated in 2003, the newest patient had liver transplantation in 2020. All patients were under immunosuppressive therapy (tacrolimus, everolimus or mycophenolat mofetil). The patients in the first six months of transplantation were also receiving steroid therapy.

Ten of the patients (55.5%) had at least one initial symptom. The most common COVID-19 associated symptom in the patients was fever. High fever response was observed in seven patients, cough in four patients, myalgia in two patients, dyspnea, nausea/vomiting and headache in one patient each. PCR positivity was detected in all but one of the symptomatic patients. Also, in seven of the symptomatic patients, COVID-19 compatible findings were detected in computed tomography of the thorax while the examination was interpreted as normal in three of them. The remaining eight patients were asymptomatic. It was understood that six of these patients had a history of COVID-19 after COVID IgG and IgM antibody tests were found to be positive in control tests. PCR and thorax CT findings were negative in these six patients, as well. While only CT positivity was detected in one of the remaining two patients, there was no symptom in the other patient although both PCR and CT were positive for COVID-19.

Six patients who were diagnosed with antibody positivity continued to be followed up in their current state without the need for treatment. Other two asymptomatic patients were hospitalized due to their CT findings and PCR positivity in one patient. Nine of the symptomatic patients were hospitalized and followed up in the COVID unit while one was followed in the COVID intensive care unit. However, the patient who was followed up in the intensive care unit was taken into intensive care because of existing liver functions, not because of the symptoms of COVID-19. Total hospitalization rate was 66.6%. Except for the patients whose diagnosis was confirmed with antibody positivity, in 12 patients (including asymptomatic patients), immunosuppressive therapy was stopped if the patient was re-

Table 1. Symptom, examination and treatment data of COVID-19 positive liver transplant patients

	Trans.	Symptoms	CT finding	PCR	Antibody	Treatment
Patient 1	CLT	Fever Nausea Vomiting	None	Positive	-	Hydroxychlorine
Patient 2	LDLT	Fever Cough	Positive	Negative	-	Favipiravir Hydroxychlorine
Patient 3	CLT	None	None	Negative	Positive	None
Patient 4	CLT	None	None	Negative	Positive	None
Patient 5	LDLT	None	None	Negative	Positive	None
Patient 6	CLT	Cough Dyspnoea	Positive	Positive	-	Favipiravir Hydroxychlorine
Patient 7	LDLT	Coguh	None	Positive	-	Favipiravir Hydroxychlorine
Patient 8	LDLT	Fever Cough Myalgia	Positive	Positive	-	Favipiravir Hydroxychlorine
Patient 9	LDLT	Fever Cough	None	Positive	-	Favipiravir Hydroxychlorine
Patient 10	LDLT	Fever Cough	Positive	Negative	-	Favipiravir Hydroxychlorine
Patient 11	LDLT	None	Positive	Negative	-	Favipiravir
Patient 12	LDLT	None	Positive	Positive	-	Favipiravir Hydroxychlorine
Patient 13	CLT	None	None	Negative	Positive	None
Patient 14	CLT	Fever	Positive	Positive	-	Favipiravir
Patient 15	CLT	Fever Cough	Positive	Positive	-	Favipiravir Hydroxychlorine
Patient 16	CLT	None	None	Negative	Positive	None
Patient 17	CLT	None	None	Negative	Positive	None
Patient 18	LDLT	Headache	Positive	Positive	-	Favipiravir

LDLT: Living donor liver transplantation, CLT: Cadaveric liver transplantation.

ceiving mycophenolate mofetil, and other immunosuppressive treatments were continued to be used by reducing the daily dose without discontinuation. A standard protocol is followed in our center for the treatment of COVID-19. After laboratory values of the patients were evaluated, these patients were hospitalized and treatment was started. All patients were isolated and hospitalized in COVID units. These patients received only favipiravir (standard treatment for five days) if there was pneumonic infiltration or hydroxychloroquine (standart treatment for five days) if not. Anticoagulant therapy was initiated in all patients. After the treatments were completed, if the patient's COVID-19 PCR test result was negative, COVID treatments were discontinued and immunosuppressive treatments were continued as in pre-illness doses. COVID-19 related mortality was not observed in any of the patients.

During the pandemic period, 12 liver transplant operations were performed in our center. Nine of them were living donor liver transplantation and the remainder were cadaveric liver transplantations. In these nine living donor liver transplant patients, five donors were first degree, one donor was second degree and two donors were third degree relatives while the donor of one patient was non-relative. Two of our patients got COVID-19 positive during this period. One of them was asymptomatic, but there was thorax involvement on CT scan. The other patient had COVID before transplantation and was followed up in the intensive care unit due to liver failure. Both patients received favipiravir therapy. While the patient who had COVID after transplantation was discharged after COVID-19 treatment, the patient who was transplanted after COVID treatment was followed up in the intensive care for a long time and was lost

even if it was not related to COVID-19. Similarly, two donor cases had COVID-19, one pre-transplant and one in post-transplant period. Two patients were discharged after their treatment.

DISCUSSION

In patients with solid organ transplantation, the rate of COVID-19 infection is higher than the general population, which was also the result in our study (12.6%). However, despite this high rate, short-term results are similar to the general population (13,14). There is a hypothesis that immunomodulators have a protective effect against the excessive and uneven inflammatory effect of COVID-19. In the study published by Belli LS et al., tacrolimus has been associated with decreased mortality for liver transplant recipients compared to other immunosuppressants (cyclosporine, mycophenolate mofetil, mTOR inhibitors) (11). TNF antagonists, not being risk factors for severe COVID-19, also supports this opinion in inflammatory bowel patients receiving immunosuppressive therapy (15). However, it is thought that similar effects may not be present in all immunosuppressants in these studies. Almost half of the patients in our study were asymptomatic patients. Nonetheless, the reason for high rate of hospitalization was due to the uncertainty about the treatment approach in this patient group and the extra care shown to these patients.

There are also opposing publications stating that mortality associated with COVID-19 is high in transplanted patients (16-18). However, in these publications, different organ transplantations have been subjected to same evaluation regardless of age and other comorbidities. Again, Belli LS et al. have shown that age is the most important factor affecting mortality in transplant patients (11). Other existing comorbidities can also affect this rate. While mean age was 48.8 years in our study, there were no patients aged 65 years and over. This may have also affected our results in a good way.

Symptoms associated with COVID-19 may also vary in liver transplant patients. Although symptoms associated with fever and respiratory tract are mostly observed, atypical symptoms (diarrhea, abdominal pain) can also be observed as in the general population (19). In our study, initial symptoms of the disease were found to be similar to the general population.

During the pandemic period, the number of liver transplants has decreased all over the world. The increased risk of infection among transplant patients and the fact that the whole world is actually at risk of infection have raised concerns. However, both cadaveric and living donor liver transplantation continued partially. There are data showing that this procedure can be done safely with taking maximum precautions, but including a limited number of patients (20). Even though we do not know the long-term results, liver transplantation case reports have been reported in patients with COVID-19 infection and recovery (21).

However, despite these results, mortality risk of the disease should not be forgotten, and there is still no data suggesting that transplantation can be performed safely during the pandemic period. In the literature, lethal progressive cases have also been reported (22,23). Only one of the 12 transplant patients we performed during the pandemic period was successfully treated while having COVID-19 after the transplant. One patient underwent transplantation after COVID-19 treatment but was lost even if it was not related to COVID-19. Two donor patients were also discharged after completing their treatment. There is still uncertainty in the literature in this direction. However, we think that transplant operations can be performed safely with the current precautions provided.

One of the limitations of this study is that verbal information was obtained from all patients. Since the follow-up of the patients in the periods when they were positive for COVID-19 was not performed by us, the questions about that period were asked and answers were in the form of "yes" or "no". Although information was tried to be obtained from all patients, reverse transcription-polymerase chain reaction (RT-PCR) test or antibody test was not performed in every patient. Rauber C et al. have performed a prospective screening trial for SARS-CoV-2 RNA and anti-SARS-CoV-2 IgG infection in liver transplant recipients during the COVID-19 pandemic and found a 3.7% rate of acute or past infection (24). Although this ratio is less than our series, it is also possible for patients to experience COVID-19 without symptoms. Therefore, one might say that this number does not reflect the true incidence and may be even more. Therefore, it should be reminded that this study reflects the rate of COVID-19 that can be detected in transplant patients in our liver transplant pool and that only these patients are evaluated.

CONCLUSION

The incidence of COVID-19 is higher in liver transplant patients than in the general population. Nonetheless, mortality rates are low. During the pandemic period, liver transplantation can be continued by following general precautions.

Ethics Committee Approval: This study was approved by Ankara City Hospital No. 1 Clinical Research and Ethics Committee (Decision no: E1/1694/2021, Date: 31.03.2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.K.Ç., O.A., D.A., E.B.B.; Design – M.K.Ç., O.A., D.A.; Supervision – M.A.K., E.B.B., M.M.Ö.; Materials – O.A., Y.M.Ö., D.A.; Data Collection and/or Processing – Y.M.Ö., E.P., D.A., M.A.K.; Literature Search – M.K.Ç., D.A.; Writing Manuscript – M.K.Ç., O.A., V.Ö.; Critical Reviews – M.A.K., E.B.B., M.M.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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**ORJİNAL ÇALIŞMA-ÖZET**

Türk J Surg 2022; 38 (3): 283-288

Karaciğer transplantasyonu yapılan hastalarda COVID-19 enfeksiyon sıklığı ve klinik seyri: Türkiye’de tek bir nakil merkezinin sonuçlarıOsman Aydın¹, Muhammet Kadri Çolakoğlu¹, Volkan Öter¹, Yiğit Mehmet Özgün¹, Erol Pişkin¹, Derya Arı², Meral Akdoğan Kayhan², Mehmet Mahir Özmen³, Erdal Birol Bostancı¹¹ Ankara Şehir Hastanesi, Sağlık Bilimleri Üniversitesi, Gastrointestinal Cerrahi Anabilim Dalı, Ankara, Türkiye² Ankara Şehir Hastanesi, Sağlık Bilimleri Üniversitesi, Gastroenteroloji Anabilim Dalı, Ankara, Türkiye³ İstinye Üniversite Tıp Fakültesi, Cerrahi Anabilim Dalı, İstanbul, Türkiye**ÖZET**

Giriş ve Amaç: Bu yazıda bir karaciğer nakli merkezinde ameliyat edilen tüm hastaları değerlendirerek karaciğer nakli yapılan hastalarda COVID-19 insidansını, hastalığın seyrini ve ölüm oranını belirlemeye çalıştık. Ayrıca pandemi döneminde merkezimizde yapılan karaciğer nakli hastalarının sonuçları da sunuldu.

Gereç ve Yöntem: Karaciğer nakli merkezimizde karaciğer nakli yapılan tüm hastalarda klinikteki rutin kontrollerinde veya telefon görüşmesi ile COVID-19 öyküsü sorgulandı.

Bulgular: Karaciğer nakli ünitemizde kayıtlı 195 karaciğer nakli hastası (2002-2020) bulunmaktaydı ve bunların 142’si halen hayatta ve takip altındaydı. Pandemi döneminde polikliniğimize takip için başvuran 80 hasta Ocak 2021’de geriye dönük olarak değerlendirildi. 142 karaciğer nakli hastası arasında toplam 18 (%12,6) COVID-19 hastası tespit edildi. Bu hastaların 13’ü erkek iken, hastaların görüşme anındaki yaş ortalaması 48,8 (22-65) idi. Hastaların dokuzuna canlı donör karaciğer nakli, geri kalanına kadavradan karaciğer nakli yapıldı. Hastalarda COVID-19 ile ilişkili en yaygın semptom ateşti. Pandemi döneminde merkezimizde 12 karaciğer nakli operasyonu yapıldı. Bunlardan dokuzu canlı vericili karaciğer nakli, geri kalanı kadavradan karaciğer nakliydi. Bu süreçte iki hastamızda COVID-19 testi pozitif çıktı. COVID tedavisi sonrası nakil yapılan bir tanesi uzun süre yoğun bakımda takip edildi ve COVID-19’a bağlı olmaksızın kaybedildi.

Sonuç: Karaciğer nakli hastalarında COVID-19 insidansı genel popülasyona göre daha yüksektir. Buna rağmen ölüm oranları düşüktür. Pandemi döneminde genel önlemlere uyularak karaciğer nakline devam edilebilir.

Anahtar Kelimeler: COVID-19 enfeksiyonu, karaciğer nakli, klinik seyir

DOI: 10.47717/turkjsurg.2022.5612