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Research

Evaluation of 846 Liver Transplant Patients Infected with COVID-19 in Turkey

Türkiye'de COVID-19 ile Enfekte olan 846 Karaciğer Nakilli Hastanın Değerlendirilmesi

Yusuf Yavuz[1], Himmet Durgut[2]

[1]Health Services General Directorate, Department of Health Services Planning, Ankara, Turkey
[2]Health Services General Directorate, Department of Blood and Blood Products, Ankara, Turkey

ABSTRACT

Objective: The clinical course of coronavirus infection in liver transplant patients is not known accurately. The aim of this study was to examine the epidemiological incidence and outcomes of liver transplant patients after coronavirus disease-2019 (COVID-19) infection who have been registered in the data system of the Tissue, Organ Transplant and Dialysis Services Department.

Methods: In this study, which was designed non-interventional, retrospective, and observational; the demographic information, clinical and radiological parameters, lifetime, hospital service and intensive care requirements and length of stay of the patients who were recorded in the information systems of the Ministry of Health, have were examined. A total of 3,426 liver transplant patients who were admitted to the hospital with suspected COVID-19 in Turkey between April 2020 and April 2021 were included in the study.

Results: Between April 2020-April 2021, 3,426 cases of liver transplant who admitted to hospitals with symptoms of COVID-19 infection in Turkey were examined. The ratio of patients diagnosed with COVID-19 infection was 24.69% (846), with a mean age of 52.3%. The 13.48% (462 people) of 3,426 people who had liver transplants were hospitalized. The mean age of the hospitalized patients was 46.6, and the average length of hospital stay was 8.64 days. When the thorax computed tomography scans of 3,426 people with suspected COVID-19 and liver transplant were examined, pneumonia was detected in 344 (10%) people and they were treated as an inpatient. The mean age of the patients with pneumonia was 59 years. The number of liver transplant patients who died was 108 (3.1%), with a mean age of 65 years. The ratio of follow-up in the intensive care unit for organ transplant recipients was 0.32%, and 0.26% of them were intubated patients.

Conclusion: Despite the use of immunosuppressive drugs in patients with liver transplant, the requirement for intensive care and the length of stay in the intensive care unit was found to be low, and the importance of strict follow-up and treatment in such patients was recognized once again.

Keywords: COVID-19, liver transplant, mortality

ÖZ

Amaç: Karaciğer nakli olan hastalarda koronavirüs enfeksiyonunun klinik seyri tam olarak bilinmemektedir. Bu çalışmadaki amaç; Türkiye'de Doku, Organ Nakli ve Diyaliz Hizmetleri Başkanlığı veri sisteminde kayıtlı karaciğer nakilli hastaların koronavirüs hastalığı (COVID-19) enfeksiyonu sonrası epidemiyolojik insidans ve sonuçlarının incelenmesidir.

Gereç ve Yöntem: Girişimsel olmayan retrospektif gözlemsel dizayn edilen bu çalışmada; Hastaların Sağlık Bakanlığı bilgi sistemlerine kaydedilmiş, demografik bilgileri, klinik ve radyolojik parametreleri, yaşam süresi, hastane servis ve yoğun bakım gerekliliği ve kalış süreleri incelenmiştir. Çalışmaya, Nisan 2020-Nisan 2021 tarihleri arasında Türkiye'de COVID-19 şüphesiyle hastaneye başvuran toplam 3.426 karaciğer nakilli kişi dahil edilmiştir.

Bulgular: Nisan 2020-Nisan 2021 tarihleri arasında Türkiye'de COVID-19 enfeksiyonu belirtileriyle hastanelere başvuran karaciğer nakli olmuş 3.426 olgu incelenmiştir. COVID-19 enfeksiyonu tanısı konan hasta oranı %24,69 (846) olup ortalama yaşları 52,3 çıkmıştır. Karaciğer nakilli 3.426 kişinin %13,48'i (462 kişi) hastaneye yatırılmıştır. Hastaneye yatırılan kişilerin ortalama yaşı 46,6 olup hastanede kalış süreleri ortalama 8,64 gün olarak saptanmıştır. 3.426 COVID-19 şüpheli karaciğer nakilli kişinin toraks bilgisayarlı tomografi görüntülemeleri incelendiğinde 344 kişide (%10)

Address for Correspondence: Yusuf Yavuz, Health Services General Directorate, Department of Health Services Planning, Ankara, Turkey
Phone: +90 541 458 17 78 E-mail: dryusufyavuz@hotmail.com ORCID ID: orcid.org/0000-0001-8031-2992

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pnömoni saptanmış olup, yatarak tedavi altına alınmışlardır. Pnömoni saptanan hastaların yaş ortalaması 59 olarak belirlenmiştir. Karaciğer nakilli hastalarda ölen hasta sayısı 108 (%3,1) olup ortalama yaşları 65 çıkmıştır. Organ nakli olanların yoğun bakım ünitesinde takip oranı %0,32 olup, %0,26'sı entübe hastalardan oluşmaktadır.

Sonuç: Karaciğer nakli olan hastalarda immünosüpresif ilaçlar kullanılmasına rağmen yoğun bakım ihtiyacı ve yoğun bakımda kalış sürelerinin düşük olduğu saptanmış ve bu tür hastalarda sıkı takip ve tedavinin önemi bir kez daha anlaşılmıştır.

Anahtar Kelimeler: COVID-19, karaciğer nakli, mortalite

INTRODUCTION

Coronaviruses (CoV) are a large family of viruses that are frequently seen in society and can cause self-limiting mild infections, such as the common cold, to more serious infections such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). In December 2019, the World Health Organization (WHO) reported cases of pneumonia of unknown etiology in Wuhan, China. In January 2020, WHO first defined the causative agent as a novel coronavirus (2019-nCoV), and later acknowledged the name of the disease as coronavirus disease-2019 (COVID-19). WHO first described the COVID-19 outbreak as an "international public health emergency" and then declared it a pandemic on March 11, after COVID-19 cases were seen in many countries outside China, where the epidemic started. The studies on COVID-19 in our country started in January, and the first COVID-19 case was seen on March 11 (1).

Common manifestations of COVID-19 infection include respiratory symptoms, fever, cough and dyspnea. The symptoms such as headache, sore throat, runny nose, myalgia, arthralgia, asthenia, newly emerging anosmia and ageusia, diarrhea can also be seen. Although the majority of patients can be asymptomatic, in severe cases, pneumonia, severe acute respiratory tract infection, kidney failure, multi-organ failure may develop and death may occur. While the mortality rate was 11% in the SARS epidemic, 35-50% in MERS-CoV, the COVID-19 mortality rate has been reported as 3.8%. In our country, this rate was determined 2.6% as of May 2020 (1,2). However, immunosuppressed patients older than 60 years of age are at higher risk of 2019-nCoV infection and may have prolonged viral clearance (2,3). Liver transplant patients and other solid organ transplant patients are more prone to viral infections such as COVID-19 since their immunity is suppressed due to the use of immunosuppression (4).

It is been known that COVID-19 infection affects the gastrointestinal system less than the respiratory tract; the information on how it affects the liver in the gastrointestinal system is still insufficient. However, it is estimated that the main mechanism of liver damage is due to the binding of the virus to the angiotensin converting enzyme 2 receptor, which is present at a high rate in the bile ducts. It is also considered to affect other vital organs such as the heart, pancreas, kidneys and intestines in a similar manner (5,6).

The aim of this study was to examine the epidemiological incidence and outcomes of liver transplant patients after COVID-19 infection who have been registered in the data system of the Ministry of Health, Tissue, Organ, Transplantation and Dialysis Services Department in Turkey.

METHODS

Our study was designed as non-invasive, retrospective, and observational. The study was conducted using the data registered in the Tissue, Organ Transplantation and Dialysis Services Department of the Ministry of Health. Necessary permissions were obtained from the Ministry of Health for the use of the data. Demographic information, clinical and radiological parameters, life time, hospital service and intensive care requirements of the patients and accordingly, the length of stay was examined. In the study 3,426 people were included who had previously undergone liver transplantation and admitted to public, university and private hospitals in Turkey with the suspected COVID-19 between April 2020 and April 2021. As a result of these tests, 846 liver transplant patients diagnosed with COVID-19 have been evaluated. In the study for the diagnosis of patients considered as COVID-19 those with positive real-time fluorescent real-time polymerase chain reaction (RT-PCR) detection of 2019-nCoV nucleic acid or those with positive serum 2019-nCoV-specific IgM antibodies were acknowledged as infected by COVID-19 infection. It was not considered COVID-19 if two consecutive tests of 2019-nCoV nucleic acid (sampling time at least 24 hours apart) were negative and 7 days later, the IgM/IgG antibodies specific for 2019-nCoV were still negative. 2019-nCoV nucleic acid detection; it was preferred in

nasopharyngeal swabs, sputum, other lower respiratory tract secretions (sputum or airway extracts).

The study was initiated after obtaining the approval of the Ankara City Hospital Non-interventional Clinical Research Ethics Committee with the decision number E2-21-244 (date: 10.03.2021). Our study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments.

Statistical Analysis

Liver transplant patients statistics for each year were recorded on the tabulation software and the frequency changes were calculated using the statistical formulas of the tabulation software. Patient consent was waived because of the study.

RESULTS

Between April 2020 and April 2021, 3,426 liver transplant patients with COVID-19 symptoms or suspected COVID-19 in Turkey were analysed. Among these cases, 1,576 (46%) were female and 1,850 (54%) were male. The mean age of men was 48.3, the mean age of women was 46.6. Among these liver-transplanted cases, 24.69% (846) were diagnosed with COVID-19 infection with positivity of real-time fluorescent RT-PCR detection or serum 2019-nCoV-specific IgM antibodies.

Among the patients diagnosed with COVID-19 infection, 338 (39.9%) were female, 508 (59.5%) were male, with a mean age of 52.3. The 53.9% (456 people) of 846 liver transplant patients diagnosed with COVID-19 infection were hospitalized. The mean age of the patients who were diagnosed with COVID-19 infection and then hospitalized and followed up for the disease was 48.6 years, and 286 (62.2%) of these patients were male and 170 (37.8%) were female. The hospital stay of liver transplant patients was between 3 and 35 days, with an average of 8.64 days.

When the thorax computed tomography (CT) scans of 846 liver transplant patients diagnosed with COVID-19 were examined, pneumonia was detected in 347 (41%) patients and they were treated as inpatients (Figure 1). Among these patients diagnosed with pneumonia, 202 (58.21%) were male and 145 (41.79%) were female. In addition, the mean age of these patients with pneumonia was 58.3 years.

Among the patients diagnosed with COVID-19 infection and hospitalized because of the disease, the number of patients followed up in the intensive care unit was 94 (11.1%). The mean length of stay in the intensive care unit was 7.88 days, and the mean age of these patients was 63 (Figure 2).

Among the 94 patients hospitalized in the intensive care unit, 67 (71%) were intubated. The length of stay in the intensive care unit of these intubated patients was 7.88 days. When all the patients hospitalized in the intensive care unit were examined, there were only 2 patients under the age of 50 and 22 patients over the age of 70.

The number of patients who died in the intensive care unit or in the emergency and service follow-ups was 108, and the mean age of these patients was 64.4. This ratio was 8.1% among patients diagnosed with COVID-19. Among the patients who died, 62 (57.4%) were male and 46 (42.6%) were female.

DISCUSSION

Although data on liver transplant patients are limited, there is a concern that immunosuppressed patients are at a higher risk of morbidity and mortality because of COVID-19 infection. It has been estimated that transplant recipients may have a greater viral load and have more infections (4-7).

While in our country the rate of patients diagnosed with COVID-19 infection in the general population was 8.1%, within the same period the rate of patients diagnosed with COVID-19 infection among the liver transplant patients was found to be 24.69%, which was significantly higher than the general population.

Similar to the study by Colmonero et al. (7) in Spain, there was a homogeneous distribution of cases in the geographical regions. Also, in the same study, although 111 (0.82%) of 13.450 liver transplant patients in Spain were diagnosed with COVID-19, 846 (0.80%) of 10,520 liver transplant patients were diagnosed with COVID-19 in our country (7).

Lung CT is the recommended imaging procedure for diagnosing pneumonia. The imaging findings of COVID-19 are similar to those of other viral pneumonias. In the early stage, interstitial changes with multiple small patchy shadows and prominent extrapulmonary bands are seen. Multiple ground-glass shadows and lung consolidation occur in the progression phase. Compared to the general population, liver transplant recipients have more widespread lung lesions, multiple lesions, and more lower lobe involvement (8).

When the data of the Ministry of Health were examined, the average of COVID-19 pneumonia was 4.8% in the general population, however, within the same period when the thorax CT scans of liver transplant patients were examined, pneumonia was detected as 10%. In the study by Lee et al. (8), although the hospitalization rate of COVID-19 patients with liver transplant was determined as 33%, in our country,

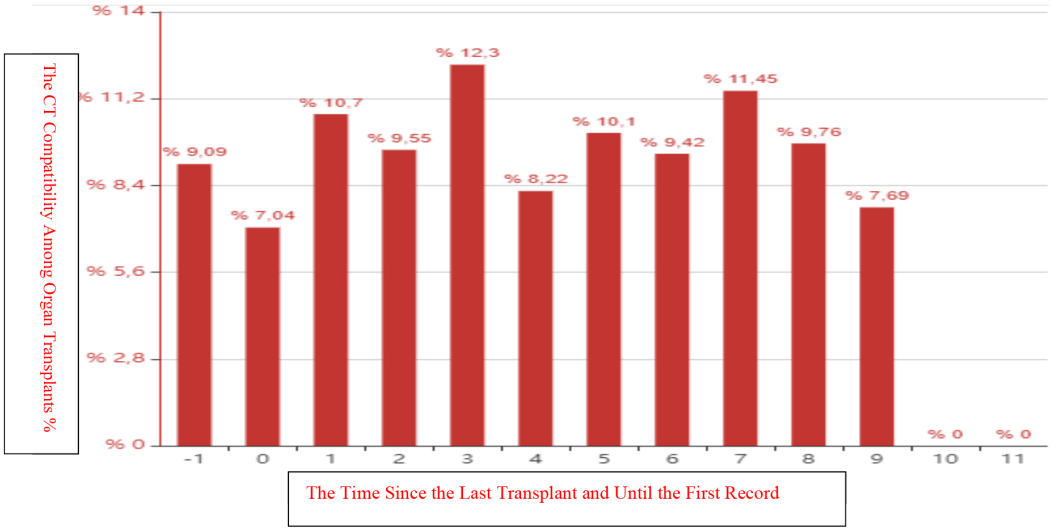

Figure 1. The CT compatibility % among organ transplants. The time since the last transplant and until the first record
CT: Computed tomography

this rate was determined to be higher than 54% because of the strict follow-up of liver transplant patients with COVID-19 infection. While all liver transplant patients diagnosed with COVID-19 in our country were hospitalized or followed up regardless of their symptoms, it has been reported in the literature that the duration and rates of hospitalization are higher in elderly liver transplant patients with COVID-19 (4). While the number of patients who died among liver transplant patients was 108 (3%), the rate of follow-up in the intensive care unit was 0.31%, and the rate of intubated patients was 0.28%, when the data of the Ministry of Health for the same period was considered, the mortality rate of COVID-19 in the general population was 2.6%, the rate of follow-up in intensive care units was 0.78%, and the rate of intubated patients was 0.56% (2-4).

When the published reports on COVID-19 were reviewed, among the risk factors for mortality; while advanced age and male gender were present, immunosuppression is not mentioned and deaths have not been reported to be correlated with other conditions requiring transplantation or immunosuppressive therapy (9,10).

In the study by Lee et al. (8), although it was stated that immunosuppression treatment would make a positive contribution by reducing the inflammatory response, they have mentioned that it may be more mortal in terms of causing hepatitis-related liver degeneration, fungi and susceptible conditions for other infections that will occur over time.

However, in the study by Gavriilidis and Pai (11), it was considered that immunosuppression may be effective for reducing mortality rates, and in accordance with our study,

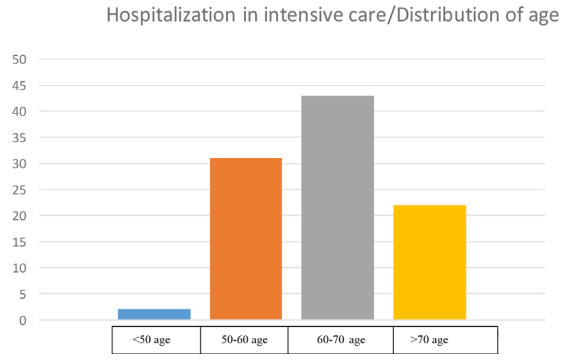

Figure 2. Under the age of 50 years, 50-60 years of age, 50-60 years of age, over the age of 70 years

it was observed that the mortality rate was lower in liver transplant patients compared with the normal population with COVID-19.

Although the susceptibility to infection has increased among liver transplant patients with COVID-19 who were immunosuppressed and under follow-up, as indicated by Choudhury et al. (12), with good care and strict follow-up there was no significant increase in the risk of death compared to the general population.

According to the study by Belli et al. (9), mortality rates in liver transplant patients with COVID-19 were more common in male patients over 60 years of age. In our study, the mean age of 108 deceased patients was 64, and 19 these patients were over 70 years of age, and 14 of them were male. The study by Verma et al. (10) indicated that the incidence of COVID-19 in liver transplant patients was lower than the normal population. In our study and many studies in the literature, among liver transplant patients like other transplant patients COVID-19 infection, COVID-19

pneumonia, and correlated hospitalization rates were higher than the general population in the world and in our country (4,13,14). When the studies on organ transplantation in many countries were examined; although the risk of contracting the disease, COVID-19 pneumonia case rates, and hospitalization rates being higher compared to the general population is a common outcome, the facts that distinguish our study from other studies were less mortality, less need for intensive care and shorter length of stay in the intensive care unit in our country.

CONCLUSION

Although the risk of transmission of COVID-19, PCR positivity and the presence of pneumonia were higher in liver transplant patients compared to the general population, the patients who were followed up and treated regularly in liver transplant centres in our country because they had been kept under control in a hospital environment or had strict follow-up and successful treatment process regardless of their symptoms, it has been observed that the need for intensive care and the length of stay in the intensive care unit in these patients diagnosed with COVID-19 was less compared to the patients in the general population.

As a result, it has been concluded that, if necessary, follow-up is made and precautions are taken this disease despite the use of immunosuppression can be kept under control in liver transplant patients.

Acknowledgments: This study was derived from the corresponding author's dissertation (date: July 2014. "The Evaluation of 846 Liver Transplant Patients Infected with COVID-19 in Turkey")

ETHICS

Ethics Committee Approval: The study was initiated after obtaining the approval of the Ankara City Hospital Non-interventional Clinical Research Ethics Committee with the decision number E2-21-244 (date: 10.03.2021). Our study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments.

Informed Consent: Patient consent was waived because of the study.

Authorship Contributions

Surgical and Medical Practices: Y.Y., Concept: H.D., Design: Y.Y., Data Collection or Processing: Y.Y., Analysis or Interpretation: H.D., Literature Search: Y.Y., H.D., Writing: Y.Y.

Conflict of interest: No conflict of interest was declared by the authors.

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