

Management of COVID-19 in Liver Transplant Recipients with Immunosuppressant Therapy: Experiences of an Iranian Transplant Registry

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Research article

Keywords: COVID-19, Liver Transplant Recipients, Immunosuppressant

Posted Date: September 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-62369/v1>

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Version of Record: A version of this preprint was published at Experimental and Clinical Transplantation on June 3rd, 2021. See the published version at <https://doi.org/10.6002/ect.2020.0526>.

Abstract

Background: Following the pandemic of COVID-19 and the increased COVID-19 risk in transplant patient receptions, the authors assessed the prevalence, clinical course, and the outcome of the COVID-19 infection among liver transplant receptions.

Methods: By designing and the use of researcher made questionnaire and the use of medical services, liver transplantation recipients under our center surveyed in terms of COVID-19 infection.

Results: Seven patients infected with COVID-19 were identified from 265 liver transplantation recipients. The majority of patients were male and had COVID-19 despite being in-home quarantine. All patients received immunosuppressive drugs during infection with COVID-19 with no change in the routine immunosuppressive therapy. Among the identified patients, 5 recovered and 2 died. One of the dead patients, in addition to having a liver transplant, suffered brain cancer with metastasis to the lungs.

Conclusion: It seems that the in liver transplants infected with COVID-19, the immunosuppressive drugs causes mild to moderate illness, and even recover from the disease.

However, more evidence is needed to prove this hypothesis. It is also recommended that transplant recipients should be warned about personal hygiene and closely be monitored by organ transplant centers.

Background

In late December 2019, COVID-19 spread as an emerging infectious disease in Wuhan, China, and quickly spread to the other countries around the world (1). With the spread of the disease worldwide, Iran was the second country that report COVID-19 cases in February 2019 (2). Since patients with underlying diseases, including transplant recipients are more prone to infection, they are expected to be at higher risk for COVID-19, experience different clinical signs and clinical courses, and possibly have high mortality and morbidity (3).

A review of the articles published since the launch of the COVID-19 pandemic in transplant patients shows that due to low immunity, especially cellular immunity, as well as fear of COVID-19 infection, observing home quarantine, hand hygiene and social distance has been high in these patients, and patients who were infected with COVID-19 had a milder clinical courses and recoverd soon (4–7). However, liver transplants are expected to have high rates of infection and mortality due to reduced immunity because of using immunosuppressants after organ transplantation (6,7). But recent reports have shown that these patients are not at increased risk for pulmonary infection compared to the general population. For example, some of the studies have shown the recovery of liver transplants from COVID-19, and few of them reports patients death (8,9). The studies have conflicting results about the clinical course of COVID-19 disease, the use or stopping of immunosuppressive drugs, and mortality rates (10,11).

Liver transplant patients' care during the SARS-CoV-2 epidemic has been challenging due to the urgent need to redistribute resources to other parts of the health care system. The existing guidelines recommend that transplant care should be reorganized and the transplant centers should be prepared to prevent the spread of disease across the transplants community and reduce organ transplants mortality (12). But scientific information related to the care of transplant patients during the SARS-CoV-2 epidemic are not sufficient (13).

On the other hand, due to the low hospitalization statistics of these patients and limited reports from transplant centers, there is not much information about the prevalence, clinical course and treatment of transplant patients infected with COVID- 19 (14). Therefore, it is hoped that by providing more studies from different countries, we could achieve acceptable and definite results regarding the prevalence, clinical course and necessary therapeutic interventions for these patients. Therefore, this study was designed to report the treatment process of Iranian Liver Transplant Registry with COVID- 19 infection. We hope the information in this paper could help health care team in reaching a unique protocol for management of these patients.

Methods

Research field

In April 2017, Tabriz University of Medical Sciences has launched the Organ Transplant Centers for transplantation of liver, kidney, heart and bone marrow in northwestern of Iran. The organ transplant centers were located in Imam Reza and Heart Shahid Madani Hospital as a training and research centers at Tabriz University of Medical Sciences. Correspondingly the Transplant Registry was established in order to coherence the organ donation and transplantation, upgrade the therapeutic and educational services to the patients. In 2019, this center obtained ID [≠ 64510] from the Deputy of Research and Technology of Tabriz University of Medical Sciences.

Following the pandemic of COVID-19 in the world, the liver transplant center examined 380 liver transplant recipients in terms of COVID-19, using a designed questionnaire, physical examination, and laboratory and paraclinical examinations.

Questionnaire

The literature review, Health Protocols of Iran's Deputy Health Minister related to COVID-19 (15), pilot study, and brainstorming were used to design the questionnaire. The content validity of the questionnaire was verified through a survey of faculty members based on Waltz & Bausell methods (16,17) to determine its content validity and Lawshe method was used to determine the content validity ratio. It was used to judge the experts on each item, using three spectrum '1 = item is required, 2 = item is useful but not required, 3 = item is not required'. Items with a content validity ratio of more than 0.62 were considered important based on the Lasha table and the number of evaluators. A method effect was used

to check the scores. Eventually, a semi-structured questionnaire was provided with questions on demographic information and COVID-19 symptoms. (Appendix 1).

The questionnaires were completed by telephone interviews, face to face interview with referred patients and their relatives to the centers, using records of hospitalized patients, performing clinical examinations and paraclinical tests by a specialist.

Patients

The study population included 380 liver transplant patients. Patients were surveyed by members (S. Z and V. L) based on a questionnaire over a period of 20 days from 18 April to 9 May 2020. Patients who were suspected to have COVID-19 were referred to Imam Reza General Hospital for definitive diagnosis by a medical team based on symptoms, clinical examination, laboratory tests, Real-time PCR test, and a chest CT scan. Any person with at least one of the symptoms (listed at Appendix 1) was considered as suspected cases for COVID-19.

Statistical analysis

Descriptive statistics, including frequency, percentage, mean, median, standard deviation, minimum and maximum are used to describe the data using SPSS.21.

Results

Sampling

Out of 380 liver transplant patients, 265 patients participated in this study. (Fig. 1) According to the results of the investigation, 200 patients had no symptoms of viral infection. Sixty patients were suspected of having COVID-19 and five of them had a definite diagnosis of COVID-19 disease. Four of the infected patients were hospitalized at Imam Reza hospital and one of them was cared at home. The most common symptoms of COVID-19 in these patients were headache, anorexia, myalgia, fatigue, diarrhea, vomiting, and cough. The demographic characteristics and clinical courses of seven patients with COVID-19 are presented at Table 1 &2.

Case presentation

Seven patients out of 265 participants were identified with COVID-19. The majority of the patients were men with a median age of 64 (44–74) years. All of the patients were Muslim, Azeri-Turkish, married, and resident at Tabriz.

All patients underwent liver transplantation following liver cirrhosis. The median time after liver transplantation was 60 months with a range of 30 to 156 months. Patient No. 4 had a history of kidney transplantation from 6 years ago, and a history of brain cancer with recent lung metastasis. Patients No.

1 and 2 had a history of hypertension from 10 years ago and Patients No. 6 also mentioned a history of ulcerative colitis from 8 years ago.

The median of diagnosis time was 7 (3–14) days for all patients. Two patients were initially diagnosed with a common cold due to runny nose, nasal congestion, and hoarseness, which in both cases, the disease was diagnosed late which the mean time of diagnosis of COVID-19 in these patients was 12 ± 8.2 days in comparison with other patients which was 7.57 ± 3.55 days.

All patients have been in quarantine since late February 2020 and have no history of hospitalization, referral to the clinic, or travel, and have not met anyone except first-degree relatives. Three patients (Patients No. 3, 5, and 6) had a history of colds among their children, and the mothers of patients No. 5, and 6 had COVID-19, that the mother of No. 5 died following a respiratory arrest and the mother of No. 6 recovered after seven days hospitalization. Other patients do not mention any contact with a suspected or infected person.

In patient No. 1, the onset of symptoms was a dry cough, followed by shortness of breath and fever. In patients 2 and 3, the initial symptoms were runny nose, hoarseness, and nasal congestion, which is followed by a sputum cough and dyspnea. For the patient NO.4, the onset of symptoms was a dry cough and myalgia, followed by chest pain, dyspnea, and a sputum cough. Patient No. 5 experienced a sputum cough followed by a dry cough. Patient No. 6 started with fever and chills, lethargy, anorexia, and myalgia, and ended with a dry cough and dyspnea. Finally, in patient NO. 7, the only symptom was fever.

Dyspnea has been observed in almost all patients and gastrointestinal symptoms have not been observed in any of the patients.

All patients were alert at the time of admission; however, all hospitalized patients with COVID-19 had low level of SPO₂. Patient No. 2 refused to accept hospitalization despite having respiratory symptoms like dyspnea, cough, and decrease in SPO₂. He preferred to be at home quarantined under the supervision of an infectious disease specialist.

The results of physical examination are shown in Table 2. The chest CT scan was positive in all patients. Blood counts in most of the cases showed an increase in AST and ALT without leukopenia. The laboratory results are shown in Table 2.

The median of the length of in-hospital stay was 8.50 (1–22) days. The dead patients were first admitted to the general ward then were transferred to the ICU due to dyspnea and a drop in SPO₂. One of the dead patients also had brain cancer with lung metastasis.

Hydroxychloroquine and azithromycin have been used for all patients along with immunosuppressant therapy without any changes in their dosage. All patients received immunosuppressive drugs with the same dosage as they used before COVID-19 diagnosis. Of the 7 patients, 2 patients (28.5%) died and 5 patients (71.5%) recovered. After discharge, patients were required to stay at home quarantine for 14 days.

Discussion

In this study, the liver transplant recipients were surveyed in terms of COVID-19. Although a number of patients did not participate in this study due to the fear of COVID-19; however, 7 patients were identified with COVID-19 among liver transplant recipients.

One of the most important findings of this study is the continuation of treatment with immunosuppressive drugs with the same dosage before getting COVID-19, which despite the weakening of patients' immune systems by these drugs, they were able to recover and get rid of COVID-19. Even one patient was treated at home and recovered.

Therapeutic principles are unclear for transplant patients with COVID-19, when cytokines have been caused acute respiratory failure. There is a considerable variability in the use of immunosuppressive drugs. Some articles have recommended to discontinue or reduction in immunosuppressive drugs dosage (13,18). Some other studies recommended to continue immunosuppressive therapy during COVID-19 infection (6,7). All of these studies reported recovered patients from COVID-19.

Most of the patients in this study were male, with a mean age of 61 years. In a systematic review study that was conducted by Lovato *et al.*, 1556 patients with COVID-19 were examined for demographic characteristics and clinical signs where the ratio of men was higher than women (16). In the study of Zeng *et al.*, the frequency and mortality were higher in men than women infected with COVID-19, which was associated with the difference in the level of COVID-19 IgG antibody between two sexes (17). In the study of Niu S *et al.*, older people with COVID-19 has a greater susceptibility to infections and mortality than younger. Another factor that had been influenced the mortality rate of COVID-19 was underlying medical conditions of patients that led to their hospitalization, intensive care and mechanical ventilation necessity (18).

In February 2020, a study has been performed on 221 patients with COVID-19 in Wuhan University Hospital which showed a high chance of contamination in older men (4). Old age, male sex, and underlying diseases have emerged as risk factors for COVID-19. The results of these studies were similar to the results of our study with differences in the ratio of males to females and the mean age.

In two cases, a definitive diagnosis was made later due to the similarity of the COVID-19 symptoms with common cold symptoms. The clinical symptoms range from relatively mild (similar to the common cold) to severe (bronchitis, pneumonia, and renal failure) in COVID-19 (5, 6). These symptoms may be intensified by other diseases or taking immunosuppressive agents and patient show atypical symptoms. Due to the similarity of COVID-19 symptoms with a common cold, participants do not consider necessary precautions and even referring to a healthcare center. Delayed diagnosis has led to the complications of the patients' condition and transfer of the disease to the other family members. Therefore, it is necessary to explain all clinical symptoms for the general public, and medical staffs.

In this study, the mean time after transplantation was 5 years and mortality rate was 28.5%. In a systematic review conducted by Nacif *et al.*, on 39 transplant patients with 16 liver transplant patients, the mean time after transplantation was 4 years for all patients and 5 years for liver transplant patients (19). In this study, the mortality rate for all transplant patients and patients with liver transplants was 26% and 38%, respectively. The mortality rate was 5% -10% in other patients of any certain underlying medical conditions (8, 9). The presence of older patients and patients with underlying diseases in the current study may lead to this difference. In the study of Muller X *et al.*, the mean length of hospital stay was 14 days, which was 9 days for our patients (20). A Survey on the patients' history of COVID-19 showed that despite staying at home, not traveling, and avoiding crowded places during quarantine they infected with COVID-19. However, all of them have mentioned the communication with first-degree relatives. Due to a lack of information on the principles for the standardization of quarantine, they have not to regard essential items such as maintaining distance and health items. It seems that quarantine principles are not yet fully understood by many people. Many patients with COVID-19 infection may be asymptomatic or present cold-like symptoms and thus lead to transmission of virus. Consequently, sharing and evaluating the quarantine principles is necessary (11, 12).

In the current study, Chest CT scan has shown lung involvement in all cases, even in a person with no signs of respiratory distress. In one case, Real-time PCR was negative, despite lung involvement in CT scan. It appears to achieve a definitive diagnosis, the use of laboratory tests and radiological imaging as well as taking an accurate history and clinical examination is required. Muller X *et al.*, also has emphasized on this issue and expressed satisfaction at the sensitivity of chest CT scan for the diagnosis of asymptomatic and symptomatic patients infected with COVID-19 (20).

Conclusions

Based on the findings, it can be concluded that the use of immunosuppressants not only did not increase mortality but also seems to have a positive effect on reducing the severity of the disease and clinical course. However, due to the fact that the low mortality of these patients has not been studied, it is not possible to have a definite opinion on the effect of immunosuppressants. Therefore, it is suggested to conduct studies with a large sample size in order to achieve a definite opinion in this case by analyzing the results of the studies. To achieve a definitive diagnosis, the use of clinical signs, laboratory and paraclinical tests are essential.

Given that patients were in contact with their families at the time of home quarantine to prevent COVID-19, which also caused them to become infected, it seems that the quarantine principles are not clear to the patients. As a result, the principles of quarantine need to be fully explained and advised to prevent contact with family members. Communications should be done in a short time and by observing the distance and observing the health points. Education through mass media can play an important role in breaking the chain of disease transmission.

Limitation

The main limitation of this study was the lack of access to all liver transplant patients and their evaluation for COVID-19, which has led to a study with a small sample size. Another limitation of the study is the generalization of results to all liver transplant recipients due to the small sample size.

In addition, in this study, we did not examine all transplant patients, including asymptomatic ones, due to financial constraints and not going to the hospital for fear of infection.

Abbreviations

ARDS: Acute respiratory distress syndrome, COVID-19: Corona Virus Disease 2019, CT: Computed Tomography, ICU: Intensive care unit, RT-PCR: Real-time polymerase chain reaction, SARS: Severe acute respiratory syndrome, SPO₂: Peripheral capillary oxygen saturation.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee in Research of Tabriz/Iran University of Medical Sciences (decree number: TBZMED.REC.2020.423) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Patients' examination and data collection were performed after approval by the deputy of research of Tabriz University of Medical Sciences, gaining the ethical code, and obtaining permission from the head of Imam Reza Hospital, patient and the head of Transplant Registry (ID# 64510). The written consent was obtained from the patient before starting the report. Informed consent, and written informed consent were obtained from legal guardians. Verbal informed consent was obtained prior to the interview.

Consent for publication: The participants have consented to the submission of the report to the journal. Patients signed informed consent regarding publishing their data.

Availability of data and material: The data are confidential and are only available to the first and corresponding authors in the Liver and Gastrointestinal Diseases Research Center, and Organ Transplant Registry of Tabriz University of Medical Sciences, Tabriz, Iran.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Authors' contributions:

Selection of title: SZ, AT, KF, and VL. Designing of the study: SZ, AT, KF, and VL. Taking ethical code: SZ, and VL. Preliminary examination of patients: SZ, FA, and VL. Examination of patients: AT, and KF. Data collection: SZ, KF, and VL. Interpreting the data: SZ, AT, KF, FA, and VL. Statistic analysis: VL, and FA. Writing of study: SZ, AT, FA, and VL. Preparing of Fig and Table: SZ, AT, and VL, and VL: Editing the study. All authors read and approved the final manuscript.

Acknowledgments: We would like to thank staffs of, Liver Transplant Center of Tabriz University of Medical Sciences, Organ Transplant Registry (ID: 64510) and the participants for taking part in the research process.

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Tables

Due to technical limitations, table 1 & 2 is only available as a download in the Supplemental Files section.

Figures

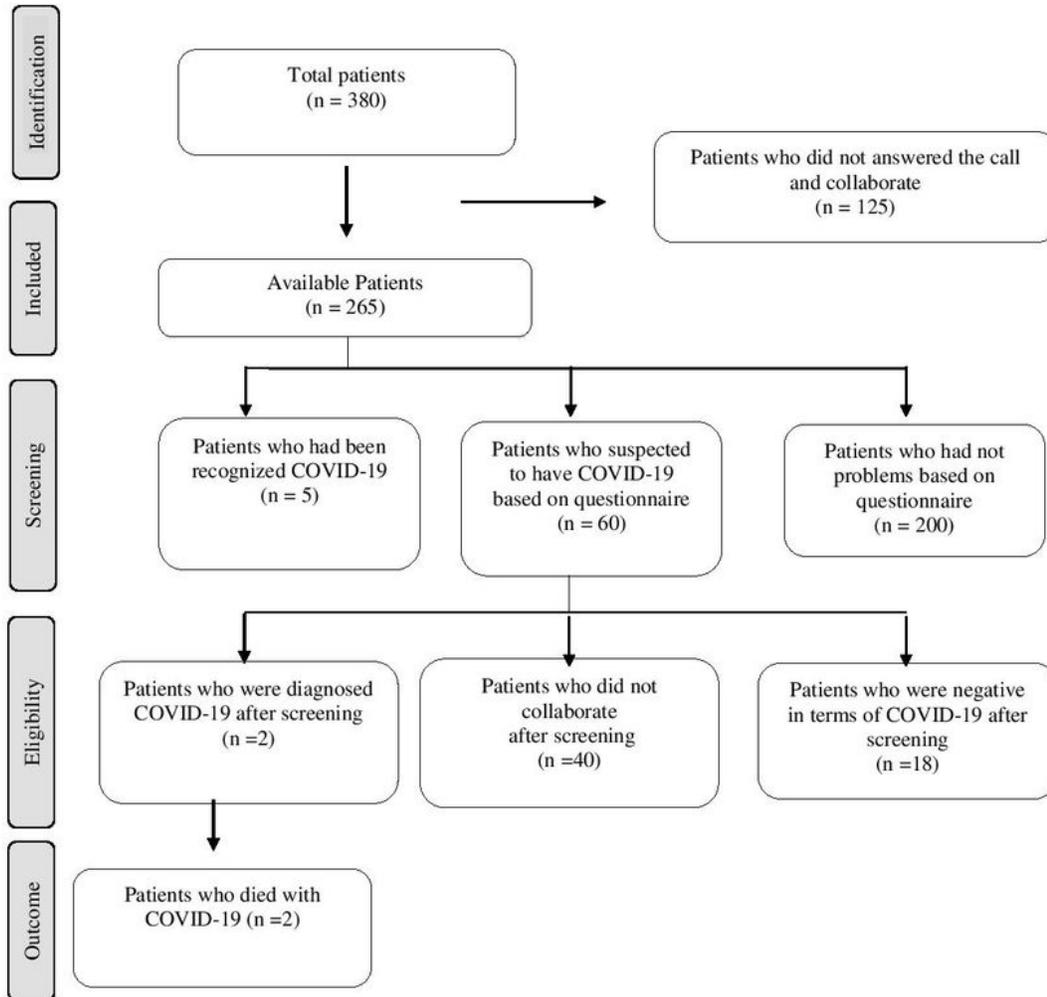


Figure 1: Flow diagram of liver transplanted patients who screened in terms of COVID-19 based on designed questionnaire.

Figure 1

Flow diagram of liver transplanted patients who screened in terms of COVID-19 based on designed questionnaire.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Tables.docx](#)
- [AppendixQuestionnaire.docx](#)