Incidence, characteristics, and outcome of COVID-19 in patients on liver transplant program: a retrospective study in the north of Iran

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Abstract

The risk of severe coronavirus disease-2019 (COVID-19) disease seems to be higher in individuals with solid organ transplantation. Therefore, the purpose of the present research is to investigate the incidence of COVID-19 and laboratory data and epidemiologic factors in liver transplant recipients and the patients on the waiting list for liver transplantation. In this study, we evaluated the records of patients on the waiting list for liver transplantation and of recipients of a liver transplant. Demographic data, underlying disease, history of drug use and participants' outcomes were collected. The diagnosis of SARS-CoV-2 infection for all patients was confirmed using a nasopharyngeal swab specimen with real-time RT-PCR. During the study period, 172 patients were enrolled, among whom 85 patients (49.4%) were on the waiting list for liver transplantation, and 87 patients (50.6%) were recipients of a liver transplant. Out of them, 10 (5.8%) had a positive result for SARS-CoV-2. Of these patients, 7.05% (6/85) and 4.6% (4/87) of patients on the waiting list and recipients of liver transplants were positive for SARS-CoV-2, respectively. Patients on the waiting list with COVID-19 infection had a higher median of albumin, ALT, AST, TBIL, DBIL, HDL and LDL value. In summary, the incidence of COVID-19 in liver transplant patients was slightly higher. The existence of underlying liver diseases should be well known as one of the poor predictive factors for worse outcomes in patients with COVID-19. So, comparative studies are recommended to identify risk factors for COVID-19 in patients with liver injury.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the factor for the development of coronavirus disease-2019 (COVID-19), initially observed in Wuhan, China, in 2019. It has had a quick spread in the world. In a similar way to this family’s previous members, COVID-19 generally results in respiratory tract infection that might be severe, asymptomatic, or mild [1–4]. The main symptoms of this disease include fatigue, fever, dry cough, and sometimes nausea, shortness of breath, vomiting, and diarrhoea. As preliminary data indicates, the severity of the disease has some predictors, such as hy-
pertension, old age, diabetes mellitus, chronic liver and kidney disease, and coronary artery disease [3–8]. The severity of the disease is mild in most patients; still, the risk of severe COVID-19 disease seems to be higher in individuals with solid organ transplantation, like liver transplants, due to receiving lifetime immunosuppressive therapy and their chronic immunosuppressed state [6,9].

Since the angiotensin-converting enzyme-2 (ACE2) receptor is present in the biliary epithelial and liver cells, the liver has been identified as a potential target for COVID-19 infection. Liver enzymes elevation is a presentation of this disease that is mainly observed in those admitted in the hospital with an incidence range of 14-53.1% [10].

The range of case-fatality rate from COVID-19 is extensive as 1–7.2%, despite the rate appearing much higher for recipients of solid organ transplants [9]. Nevertheless, the COVID-19 outcomes and epidemiology among recipient’s liver transplants are confined to case series and case reports [11]. There are few early descriptive case series and case reports of recipients of solid organ transplantation (SOT) suffering from COVID-19, suggesting poor outcomes. However, it is not known whether it is different from COVID-19 in the non-transplant population [11–14]. Various interventions were conducted in liver recipients with COVID-19, such as withdrawal and reduction of immunosuppression, treating with empirical anti-viral agents like lopinavir/ritonavir, chloroquine, umifenovir, and remdesivir, and high-dose glucocorticoids [15,16]. Thus, more all-embracing research is required for defining potential risk factors in patients with underlying liver diseases for the development of severe COVID-19.

The purpose of the present research is to investigate the incidence of COVID-19 and laboratory data and epidemiologic factors in liver transplant recipients and the patients on the waiting list for liver transplantation admitted to referral transplant centre (Razi Hospital) located in the North of Iran, Rasht, Iran.

Methods

This study was approved by the research ethics committee of Guilan University of Medical Sciences, Rasht, Iran, with number code IR.GUMS.REC.1399.135. Also, the patients’ informed consent to be allowed to use their medical information was obtained.

In this retrospective study from June to September 2020, we evaluated the records of 85 patients on the waiting list for liver transplantation and 87 recipients of liver transplant who were admitted to the referral transplant centre (Razi Hospital) located in the North of Iran, Rasht, Iran.

Of all patients, demographic data, including age, sex, past medical history and underlying disease (e.g., primary sclerosing cholangitis (PSC), diabetes, cryptogenic, Non-alcoholic steatohepatitis (NASH) and Hepatitis B (HBV)), laboratory parameters, including routine biochemical, and liver function tests data) alanine aminotransferase (ALT), aspartate aminotransferase (AST), and low-density lipoproteins (LDL), High-density lipoprotein (HDL), Vitamin D, direct bilirubin (DBIL), total bilirubin (TBIL) and albumin were investigated. In addition, history of drug use (use of antiviral drugs and immunosuppressive medications) and participants’ outcomes (death or recovery) were collected from the electronic patient files. The diagnosis of any liver diseases was confirmed via patients’ previous documents. Also, the records of subjects with considerable data lacking and lost to follow-up were excluded.

The diagnosis of SARS-CoV-2 infection was confirmed using a nasopharyngeal swab specimen with real-time RT-PCR or in subjects of negative RT-PCR, a chest computed tomography scan (CT scan) with a high level of suspicion.

Demographic data and variables as categorical variables were described as frequencies and percentages. The mean and standard deviation (SD) was carried out to describe continuous variables and qualitative data. All analyses were conducted using SPSS version 18.

Results

During the study period, 172 patients were enrolled, among whom 85 patients (49.4%) were on the waiting list for liver transplantation, and 87 patients (50.6%) were recipients of liver transplants. The mean age of patients was 47 ± 15.2. The male subjects were 49 (57.6%) on the waiting list for liver transplantation and 59 (67.8%) in recipients of liver transplant groups. Moreover, 100% and 66.7% of patients on the waiting list and recipients of liver transplants were over 45 years old, respectively.

Out of the 172 patients who were enrolled in the current study, 10 (5.8%) had a positive result for SARS-CoV-2. Of these patients, 7.05% (6/85) and 4.6% (4/87) of patients on the waiting list and recipients of liver transplants were positive for SARS-CoV-2, respectively. On the other hand, 66.7% (4/6) and 33.3% (2/6) of recipients of liver transplants with COVID-19 were over and under 45 years, respectively. All patients on the waiting list with COVID-19 were under 45 years.

Additionally, PSC was the most common underlying disease among 28.4% and 42% of the waiting list and recipients of liver transplants, respectively. Moreover, HBV, cryptogenic, hepatitis and PSC were also observed as underlying diseases in the waiting list and recipients of liver transplants. At present, 80%
(8/10) of the COVID-19 patients have recovered discharged from the hospital, and two patients (20%) died from respiratory failure: one patient from the waiting list and one from recipients of liver transplants. The demographics and details of underlying diseases are shown in Table 1.

According to results of laboratory values, patients on the waiting list with COVID-19 infection had a higher median of albumin (4.03 g/L), ALT (65.5 U/L), AST (51.2 U/L), TBIL (1.6 mmol/L), DBIL (0.61 mmol/L), HDL (66.5) and LDL (95) value compared to recipients of liver transplant with COVID-19 infection. While, albumin (4.2 g/L), HDL (48.7) and LDL (87.5) were relatively higher in recipients of liver transplant patients without COVID-19. Moreover, the mean dose of vitamin D in patients on the waiting list without COVID-19 and transplant patients with COVID-19 was 35.4 ± 20.2 and 47.1 ± 6.2, respectively, and were partially higher compared to other groups. Clinical and laboratory findings of recipients and patients on the waiting list for liver transplantation without and with COVID-19 are presented in Table 2.

As shown in Table 3, the history of drug use in liver transplant patients infected with COVID-19 was more than patients on the waiting list. The details of medication history among transplanted and patients on the waiting list for liver transplantation without and with COVID-19 are shown in Table 3.

Discussion

Since the ACE2 enzyme has a proven role in the pathogenicity of COVID-19 and due to the plentiful production of this enzyme in hepatic and biliary epithelial cells, the liver is considered as a target organ for this virus [17–19].

The Centres for Disease Control and Prevention (CDC) has stated that patients older than 65 years, and those with liver diseases are at higher risk of fatal disease [20]; therefore, regarding insufficient data on chronic liver diseases and patients with liver transplantation during the COVID-19 pandemic in our region, the aim of the present study was a descriptive study of the incidence and mortality rate of COVID-19 in liver transplant recipients and the patients on the waiting list for liver transplantation.

The results of this study showed that 5.8% of patients developed COVID-19 disease, and their mortality was 20%. Regarding mortality, specifically, it remains elevated (20%) in patients with COVID-19 in our study but comparable with those reported in the United States and Spain population, supporting the idea that liver transplantation recipients should be considered as a population at risk [21–23].

The incidence of COVID-19 in patients with liver transplantation, especially in men over the age of 45 years, was higher. Moghadam et al. also reported that since patient candidate for liver transplantation experience more stress before transplantation, more attention should be paid [24]. In this regard, Al Ghamdi et al. reported that adverse outcomes in patients with liver transplantation and the MERS-CoV virus were more common [25]. Other results of the present study showed that liver enzyme markers and bilirubin levels in patients on the waiting list for liver transplantation with COVID-19 were higher. Recent studies have reported that liver injury is mainly associated with abnormal ALT/AST levels and a relative increase in bilirubin levels, as well as a decrease in albumin levels in severe COVID-19 cases [26,27].

In addition, in a meta-analysis study, the relationship between liver damage and the severity of COVID-19 infection were studied, and the results showed that high serum levels of AST,
ALT, total bilirubin and low serum albumin levels were significantly associated with increased severity of COVID-19 [28]. However, based on the present study, ALT/AST and albumin values were high in liver transplant patients with COVID-19. In addition, patients on the waiting list for liver transplantation with COVID-19 had a higher level of ALT, HDL and LDL ratio than patients without COVID-19.

According to studies, liver damage observed in patients with COVID-19 may be due to Lopinavir/ritonavir, which is used as an antiviral drug to treat SARS-CoV-2 infection [29]. Given that liver damage can be multifactorial and heterogeneous, there is ambiguity as to whether liver damage is related to underlying liver disease or due to the use of drugs prescribed to treat COVID-19.

PSC was the most common underlying disease in both groups of patients [30]. However, HBV, cryptogenic and hepatitis were also observed as underlying diseases in the waiting list and recipients of liver transplants. Due to transplant patients have more comorbidities than the general population, the expected severity of COVID-19 would be increased [14,31]. According to the results of the present study, in general, the history of drug use was higher in patients with liver transplantation. In patients with a history of drug use, the incidence of COVID-19 was higher in liver transplant patients. The frequency of proton pump inhibitors and calcium D in liver transplant patients with COVID-19 was higher. Moreover, in patients with COVID-19, the frequency of vitamin D intake was similar and very low in both groups [32]. Alqahtani et al. (2020) investigated the association of liver damage with COVID-19. In their study, patients with coronavirus (COVID-19) disease experienced varying degrees of liver abnormalities. They suggested treatment with acetaminophen and avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) in cirrhosis, but caution to be exercised when using antiviral agents in patients

### Table 2. Clinical, laboratory of recipients and patients on the waiting list for liver transplantation without and with COVID-19

| Variable          | Transplanted (N:87) | Before undergoing a liver transplant (N: 85) | Transplanted with COVID-19 (N:6) | Before undergoing a liver transplant with COVID-19 (N: 4) |
|-------------------|---------------------|---------------------------------------------|---------------------------------|----------------------------------------------------------|
| Blood biochemistry |                     |                                             |                                 |                                                          |
| Albumin (g/L)     | 4.2 ± 0.61          | 3.7 ± 0.54                                  | 3.9 ± 0.59                      | 4.03 ± 0.21                                              |
| ALT (units/L)     | 26.7 ± 24.02        | 45.7 ± 26.4                                 | 46.3 ± 38.2                     | 65.3 ± 43.4                                              |
| AST (units/L)     | 24.7 ± 17.5         | 53.5 ± 32.9                                 | 29.3 ± 13.7                     | 51.3 ± 16.1                                              |
| TBIL (mmol/L)     | 0.98 ± 0.61         | 4.6 ± 1.8                                   | 0.54 ± 0.3                      | 1.6 ± 0.84                                               |
| DBIL              | 0.31 ± 0.19         | 0.76 ± 1.1                                  | 0.32 ± 0.13                     | 0.61 ± 0.26                                              |
| HDL               | 48.7 ± 13.9         | 46.7 ± 16.1                                 | 40.6 ± 17.3                     | 66.5 ± 19.1                                              |
| LDL               | 87.5 ± 31.6         | 84.1 ± 3.2                                  | 87.2 ± 26.5                     | 95 ± 5.6                                                 |
| Vitamin D         | 33.8 ± 18.5         | 35.4 ± 20.2                                 | 47.1 ± 6.2                      | 41.5 ± 24.04                                             |

### Table 3. Treatment among transplanted and patients on the waiting list for liver transplantation without and with COVID-19

| Variable          | Transplanted (N:87) | Before undergoing a liver transplant (N: 85) | Transplanted with COVID-19 (N:6) | Before undergoing a liver transplant with COVID-19 (N: 4) |
|-------------------|---------------------|---------------------------------------------|---------------------------------|----------------------------------------------------------|
| Prednisolone      | 64 (73.6)           | 17 (20)                                     | 2 (33.3)                        | —                                                        |
| Cellcept          | 38 (43.7)           | 1 (1.2)                                     | 2 (33.3)                        | —                                                        |
| Folate            | 52 (59.8)           | 23 (27)                                     | 3 (50)                          | —                                                        |
| Tacrolimus        | 77 (88.5)           | 2 (2.3)                                     | 2 (33.3)                        | —                                                        |
| Aspirin           | 16 (18.4)           | 8 (9.4)                                     | 1 (16.7)                        | —                                                        |
| Calcium           | 68 (78.2)           | 19 (22.4)                                   | 4 (66.7)                        | 1 (25)                                                   |
| Multivitamin      | 2 (2.3)             | 14 (16.5)                                   | —                               | —                                                        |
| Proton-Pump Inhibitor Drugs (Ppis) | 49 (56.3) | 26 (30.6)                                  | 4 (66.7)                        | —                                                        |
| Azithromycin      | 1 (1.2)             | 1 (1.2)                                     | 1 (16.7)                        | —                                                        |
| Hydroxychloroquine| 3 (3.4)             | —                                           | 2 (33.3)                        | —                                                        |
| HMG-Coa Reductase Inhibitors | 10 (11.5) | 17 (20)                                     | 2 (33.3)                        | —                                                        |
| Insulin           | 7 (8)               | 10 (11.8)                                   | 1 (16.7)                        | 1 (25)                                                   |
| Tavannex          | 3 (3.4)             | —                                           | 2 (33.3)                        | —                                                        |
| Metformin         | 10 (11.5)           | 6 (7)                                       | 2 (33.3)                        | —                                                        |
| Ursodeoxycholic Acid (UDCA) | 41 (47.1) | 28 (32.9)                                   | 2 (33.3)                        | 1 (25)                                                   |
| Mesalazine        | 11 (12.6)           | 6 (7)                                       | 1 (16.7)                        | 1 (25)                                                   |
| Levothryoxine     | 3 (3.4)             | 6 (7)                                       | 1 (16.7)                        | 1 (25)                                                   |
| Spirinoltacne     | —                   | 4 (4.7)                                     | —                               | 1 (25)                                                   |
| Sirolemus         | 1 (1.2)             | —                                           | 3 (50)                          | —                                                        |
| Propranolol       | 15 (17.2)           | 1 (1.2)                                     | 1 (16.7)                        | —                                                        |
| Losartan          | 5 (5.7)             | 5 (5.9)                                     | 1 (16.7)                        | —                                                        |
| Carvedilol        | —                   | 16 (18.8)                                   | 2 (50)                          | —                                                        |

DBIL, direct bilirubin; HDL, High-density lipoprotein; LDL, low-density lipoproteins; TBIL, Total bilirubin.
with liver problems and drug interactions after liver transplantation [27]. Niknam et al. investigated two patients with COVID-19, including a 60-year-old female patient with diabetes and a 46-year-old man who had previously had a liver transplant. Both patients recovered after starting hydroxychloroquine and continuing to use all immunosuppressive agents except mycophenolate based on the decision of the medical team with different specialities [33]. However, the existence of underlying liver diseases should be well known as one of the poor predictive factors for worse outcomes in patients with COVID-19. So, comparative studies are recommended to identify risk factors for COVID-19 in patients with liver injury [34]. However, due to the relatively small sample size of transplanted cases with COVID-19, our results could not completely represent the effect of immunosuppression on the course of the disease, so the analysis must be interpreted with caution.

In conclusion, the results of the present study showed that the incidence of COVID-19 in liver transplant patients was slightly higher. The existence of underlying liver diseases should be well known as one of the poor predictive factors for worse outcomes in patients with COVID-19. So, comparative studies are recommended to identify risk factors for COVID-19 in patients with liver injury.

Ethics approval and consent to participate

This study was approved by the research ethics committee of Guilan University of Medical Sciences, Rasht, Iran, with number code IR.GUMS.REC.1399.135. Written informed consent to participate in the study was obtained from participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Transparency declaration

The authors report no conflicts of interest in this work. Self-funding.

Authors’ contributions

Conceived and designed the experiments: PR, MSD and MTA. Performed the experiments: MNT, KM and AS. Analysed the data: RNT and KM. Contributed reagents/materials/analysis tools: RNT and SJ. Contributed to the writing of the manuscript: MTA, KM and MSD. All authors read and approved the final manuscript.

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