

# A Retrospective Study about COVID-19 in Liver Transplant Recipients: Clinical Characteristics, Hospitalization and Mortality Rates in a Single Lebanese Liver Transplant Center

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## Keywords:

COVID 19 infection; Liver transplant; Case study

## 1. Abstract

**1.1. Background:** Liver transplantation has evolved to become the definitive treatment for most types of acute and chronic liver failure. Recent studies suggest that incidence of covid-19 among this population is generally higher due to the fact of chronic immunosuppressant. However, there is a scarcity of literature describing clinical presentation, and outcomes in Liver Transplant (LT) patients with Covid-19. We aimed to describe the clinical characteristics in LT recipients diagnosed with Covid-19 who had undergone liver transplantation at the liver and kidney transplant center of Al Rassoul hospital in Lebanon.

**1.2. Methods:** A retrospective case series study conducted among patients who previously had a liver transplantation at the kidney and liver transplant center of Al Rassoul hospital in Lebanon and diagnosed with Covid-19, before the era of vaccination. Demographic information, past medical history, clinical manifestations, severity of

the disease and patient's outcome were recorded.

**1.3. Results:** During the study period, a total of 27 LT recipients were enrolled among whom 6 (22.2%) patients were tested positive for Covid-19. The majority of the infected patients were female (66.6%). Out of these patients, 83.3% had mild Covid-19. The most frequent reported symptoms were fever (66.7%). 50% of patients presented with GI symptoms. The rate of hospitalization was 50%, and no patient death was recorded. All infected patient was receiving tacrolimus as immunosuppressive therapy throughout the course of infection.

**1.4. Conclusion:** This study confirmed that liver transplant patients infected with Covid-19 had high rates of hospital admission and they were frequently presented with GI symptoms.

## 2. Introduction

Liver transplantation become the only curative treatment for end stage liver diseases [1]. The outcome of such major surgery had im-

proved significantly since the first LT surgery in 1963 due to the introduction of immunosuppressant therapy, cyclosporine and tacrolimus inhibitor, in 1979 and 1990 respectively [2]. Thus, patients with ESDL have now chance to live with better quality of life [1]. Immunosuppressant drugs decreased the rate of steroid resistant rejection and rejection related graft loss, so most of complications and causes of mortality after LT are unrelated to graft function [3], however prolonged exposure to IS predispose to a variety of life-threatening complications. It absolutely increases risk of opportunistic infections and viral related malignancies [4].

At the end of December 2019, a novel coronavirus appeared in Wuhan in China, after which it progressed rapidly to invade hundreds of countries [5]. It causes upper and lower respiratory symptoms which can progress to ARDS. All form of immunity, innate and adaptive, are crucial to control and resolve this viral infection, however, over activation of immune cells can lead to cytokine storm and ARDS [6]. A systematic review and meta-analysis of SOT recipients with SARS-CoV-2 infection from January 1st to October 9th 2020, showed that SOT recipients (including kidney, liver, heart and lung) have a high rate of hospital and ICU admission with overall mortality rate of 18 [7]. However, other prospective cohort study showed that mortality rate among SOT recipient hospitalized for COVID-19 infection is the same when compared to general population [8].

When talking about liver transplant, incidence of covid-19 among this population is generally higher due to the fact of chronic immunosuppressant, however, the mortality rate is lower [9]. Upon hospitalization, reducing or stopping mycophenolate and continuing tacrolimus inhibitors were found to be associated with increased survival among this vulnerable population [9, 10]. In addition, patients with significant liver diseases have worst outcome when infected by Covid-19. Thus, liver transplantation should only be done for patients with high MELD scores, acute liver failure and hepatocellular cancer within Milan criteria [11]. Furthermore, in case of LT surgery, both donors and recipients should be screened for covid-19 and if the results turn positive, donor should be excluded and OR should be postponed until recovery [11].

The purpose of this study is to describe the clinical characteristics of LT patients infected with Covid-19 who previously had a liver transplantation at the liver and kidney transplant center of Al Rassoul hospital in Lebanon, and to investigate the rate of hospital admission and mortality rate in this vulnerable population.

### 3. Methods

This is a retrospective case series study conducted among liver transplant patients who had undergone liver transplantation at the liver and kidney transplant center of Al Rassoul hospital in Lebanon. In this study, we reviewed the clinical data of 27 recipients of liver transplant and we identified 6 Covid-19 patients before the era of vaccination. The research ethics committee of Al Rassoul Hospital approved all aspect of the project before the start of the study.

For patients with confirmed Covid-19 infection, we extracted the

following information: demographic information (age, gender), past medical history including the indication of liver transplant, and the immunosuppressive therapy, severity of the disease, clinical manifestations including cough, fever, fatigue, myalgia, gastrointestinal symptoms, and dyspnea, the need of hospitalization, the need of oxygen, and patient's outcome (mortality rate).

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 [12].

Mild COVID-19 infection is defined as non-hospitalization or hospitalization without needs for oxygen. Moderate COVID-19 infection is defined as an oxygen saturation "SpO2"  $\geq$  94%, and evidence of lower respiratory disease during clinical assessment or imaging. Severe COVID-19, is defined as "SpO2"  $\leq$  94%, the need for oxygen, mechanical ventilation, intensive care, and/or death [13].

Data analysis was done using the Statistical Package for Social Sciences (SPSS), version 24, and simple descriptive statistics were performed. Categorical variables were represented as frequency and percentages. As for the continuous variables, mean and standard deviation were calculated.

### 4. Results

In this retrospective case series study, we identified 27 liver transplant patients, among whom 6 (22.2%) patients were tested positive for Covid-19. The mean age of the infected patients was  $30.38 \pm 13.78$  years, and 66.6% were female. 33.3% of cases undergoing liver transplantation because of autoimmune hepatitis and Wilson each. Other indications for LT were cryptogenic liver cirrhosis (16.7%), and PSC (16.6%). Finally, all patients were on tacrolimus with no change of immunosuppressant post-infection (table 1).

**Table 1:** demographic and medical history of liver transplant patients infected with Covid-19.

Demographic characteristics	
Age (mean, SD)	30.38 (13.87)
Gender, N (%)	
Male	2 (33.3)
Female	4 (66.7)
Medical history	
Cause of liver transplant, N (%)	
Autoimmune hepatitis.	2 (33.3)
Cryptogenic liver cirrhosis.	1 (16.7)
Wilson	2 (33.3)
PSC	1 (16.7)
Continue of immunosuppressant drug, N (%)	
Tacrolimus	6 (100.0)
Other drugs	0 (0.0)

SD: standard deviation. PSC: primary sclerosing cholangitis.

## 5. Clinical Symptoms.

Covid-19 was mild in 5 (83.3%) patients and moderate in 1 (16.7%) patient. No severe cases have been noted. Of the 6 patients with confirmed Covid-19, 50% were hospitalized and only 2 patients (17.6%) required oxygen support. The most common symptoms were fever (4 patients, (66.7%)), followed by fatigue (2 patients, 33.3%). Cough and myalgia were less common symptoms found in one patient each (16.3%). Half of patients were presented with gastrointestinal symptoms, and dyspnea developed in 1 patient (16.3%). Finally, no patient death was reported in this study (table 2).

**Table 2:** Clinical presentation and outcomes of LT patients infected with Covid-19.

Clinical presentation	
Severity of Covid-19, N (%)	
Mild	5 (83.3)
Moderate	1 (16.7)
Severe	0 (0.0)
Hospitalization, N (%)	
No	3 (50.0)
Yes	3 (50.0)
Need of oxygen, N (%)	
No	5 (83.3)
Yes	1 (16.7)
Fever, N (%)	
No	2 (33.3)
Yes	4 (66.7)
Dyspnea, N (%)	
No	5 (83.3)
Yes	1 (16.7)
Cough, N (%)	
No	5 (83.3)
Yes	1 (16.7)
GI symptoms, N (%)	
No	3 (50.0)
Yes	3 (50.0)
Fatigue, N (%)	
No	4 (66.7)
Yes	2 (33.3)
Myalgia, N (%)	
No	5 (83.3)
Yes	1 (16.7)
Patient's outcome	
Mortality, N (%)	
No	6 (100.0)
Yes	0 (0.0)

## 6. Discussion

In this case series study, we reported the clinical characteristics of LT patients who were diagnosed with Covid-19, and who previously had a liver transplantation at the liver and kidney transplant center of Al Rassoul hospital in Lebanon. The proportion of LT patients with Covid-19 was 22.2% (6 of 27 LT patient) which is considered high compared to reports from other countries. A study from Germany, conducted among 219 LT patients reported 3.1% confirmed cases of Covid-19 [14]. Another Colombian study of 540 liver transplant recipient, found positive Covid-19 infections in 6.2% of cases [15]. To mention that, when compared with the general population, LT patients were considered at higher risk for Covid-19 disease. The Spanish Society of Liver Transplantation (SETH) organized a nationwide prospective study [9] in which 111 Spanish LT patients infected with Covid-19 and recruited from 22 transplant center were studied. They found that the incidence of Covid-19 among patients who had received liver transplantation was almost the double of that detected in the general population [9].

It is well known, that patients who had received liver transplantation, present more comorbidities than the general population, and therefore, they may have increased risk for severe covid-19 [16]. However, in the present study, the majority of LT patient developed mild disease (5, 83.3%), only 1 patient had moderate illness (16.3%), and no patient meet the criteria of severe Covid-19 infection. Lee et al. assessed the severity of Covid-19 in 24 hospitalized LT patient admitted to a medical center in the United States, and found that 8% of patients developed mild disease, 46% had moderate disease, and 46% had severe disease [17]. A recent systematic review conducted by Kulkarni V. et al. [16] and included 1,522 COVID-19 infected LT recipients showed that about 23% of LT patients developed severe Covid-19 infections [16]. Colmenero et al [9]. found a proportion of 31.5% of LT patients with severe covid-19 infections. According to these studies, male gender, older age (< 60 years), and presence of comorbidities were considered as significant risk factors for the development of severe Covid-19 [9].

All patients in our study were on Tacrolimus, with no change of immunosuppressant post infection. Researchers suggested that during Covid-19 infection, outcomes could be improved with continued immunosuppression [18, 19]. For instance, Belli et al. [10] found in their study organized among 103 LT patients with Covid-19 and recruited from centers located in different European countries including Italy, Spain, and France, that the mortality rate decreases with the use of tacrolimus (HR, 0.55; 95%CI, 0.31–0.99). Recent studies demonstrated that the replication of CoV depends on active immunophilin pathways, and that tacrolimus by binding the immunophilin FK-506-binding proteins could inhibit viral replication. Another explanation for the protective effect of tacrolimus could be related to its immunosuppressive effects on T-cells. This causes a significant decrease in the production of many cytokines, and hence, reduction of cytokine storm observed in Covid-19 [20, 21]. The SETH cohort study

demonstrated that calcineurin inhibitors (tacrolimus or cyclosporine) reduce the risk of severe Covid-19, whereas, the use of mycophenolate drugs was associated with worse outcomes and increased risk of severe Covid-19 [9]. These findings indicate the need of more studies to determine the effect of immunosuppressive therapy among LT patient with Covid-19.

Regarding clinical presentation, fever was the most common symptom reported in 66.7% of patients, followed by fatigue found in 33.3% of patients. Other symptoms including cough, myalgia, and dyspnea were less common symptoms. Similar results have been reported by other studies. C Becchetti et al, [22] conducted an international prospective study including 57 LT patients recruited from 12 European institutions and diagnosed with Covid-19. The most common reported symptoms were fever (79%), cough (55%), and fatigue or myalgia (56%) (22). Similarly, in a recent systematic review of 35 articles including 1076 patients, fever (61.4%), cough (58.6%) and dyspnea (36.2%) were the most frequent symptoms [23]. Webb et al, [24] reported respiratory symptoms as the most frequent symptoms found in LT patient with Covid-19. This variation in the reported symptoms depends upon various factors including the study design, the study subjects, methods of collecting data, and data analysis methods.

In this study, we found that LT patients strongly reported GI symptoms, presenting in 50.0% of them. These findings were consistent with the results of a recent systematic review that showed that 3% to 79% of LT patients with Covid-19 experience GI symptoms. Reports from different countries have also described a diversity of GI symptoms in LT recipients with confirmed Covid-19. In a multi-center cohort study involving 151 LT patients with Covid-19 from 18 countries including USA (36% of patients), UK (19% of patients), Italy (15% of patients), and one Middle Eastern country (12% of patients), 30% had GI symptoms, whereas 12% of non LT patients have been found to have GI symptoms ( $p$ -value < 0.0001) [24]. Similarly, a study from 30 European countries, showed that 22.6% of 243 LT patients with Covid-19 [10].

According to some studies, recipient of solid organ transplant diagnosed with severe Covid-19 are associated with increased hospitalization rate and with higher mortality rates compared to non-transplant patients [25]. In contrast, other studies demonstrated that liver transplantation do not increase the rate of mortality in patients with Covid-19 (24). In the current study, we did not document any case of death as a result of the complication of covid-19, probably because none of our LT patients presented with severe illness. However, of note was the high proportion of LT patient who required hospitalization (50%). High hospitalization rates was also found by C Becchetti et al. (64.8%) [23], Webb al. (82%) [24], Belli et al. (84%) [10], and Colmenoro et al. (86.5%) [9]. Though, In the study of Mansoor et al. [26] 40% of 126 Covid-19 positive LT recipient required hospitalization.

This study to the best of our knowledge is the first to describe the clinical presentation, hospitalization rates and outcomes of LT patients with confirmed Covid-19 in Lebanon. Although more cases need to be studied, this study is considered an important first step in establishing the clinical characteristics of this vulnerable population.

This study is limited by its retrospective nature, small sample size, and single center experience. We are also limited to the data as were recorded by the physician who evaluated the patients, and therefore, the availability of more clinical information, may have improved the content of the study. Moreover, due to the limited sample size, we could not assess the severity and the mortality rate of Covid-19 among LT patient.

## 7. Conclusion

In summary, we have found in this study that GI symptoms were very common in LT patients with Covid-19. We also reported a high hospitalization rate among Covid-19 positive LT recipient, with no case of death. Finally, considering the limited research on Covid-19 among patients who had been previously received liver transplantation, further prospective study should be conducted to identify predictive factors associated with positive Covid-19 diagnosis among LT recipients. We also recommend further research to explore the effectiveness of immunosuppressive strategies during the course of infection in order to provide clear guidelines in this respect.

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