Original Article

Evaluation of Factors Affecting the Outcome of COVID-19 in Patients with Liver Transplantation

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ABSTRACT

Background:
In patients undergoing liver transplantation (LT), the risk of infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the severity of the consequences are almost unknown. Therefore, this study aimed to examine the influencing factors in the relationship between LT and the consequences of coronavirus disease 2019 (COVID-19).

Materials and Methods:
In this cross-sectional study, all individuals with a history of LT who contracted COVID-19 through the Liver Transplantation Clinic, Imam Khomeini Hospital Complex, Tehran, Iran, were recruited during the 2 years of the COVID-19 pandemic from March 2020 to March 2022.
The required data were extracted from patients' medical records and hospital databases. The analyses were conducted using IBM SPSS software version 22.

Results:
162 patients were studied. The mortality prevalence was 24.1%. A significant relationship was found between COVID-19 severity and the number of LTs, presence of pulmonary involvement, need for remdesivir and steroid treatment, and death. Also, a significant relationship was found between death and age at the time of LT, lung involvement, early infection (within one month after LT) with COVID-19, and the need for hospitalization due to COVID-19.
A significant relationship was found between liver enzyme disorders (elevated alanine and aspartate transferase levels [>40 U/L] and bilirubin levels [>1.5 mg/dL]) and early infection with COVID-19, severe COVID-19 involvement, pulmonary involvement, need for remdesivir and steroid treatment, and death due to COVID-19.

Conclusion:
Advanced age, pulmonary involvement, dependence on corticosteroid and remdesivir treatment, the number of LTs, and elevated liver enzyme levels were significant risk factors associated with severe COVID-19 and mortality.

Keywords: COVID-19, Liver transplantation, Prognosis

please cite this paper as:
Ziamanesh F, Kariminejad Dizbuni HR, Alborzi Avanaki F, Taher M. Evaluation of Factors Affecting the Outcome of COVID-19 in Patients with Liver Transplantation.*Govaresh* 2024;29: 150-156.

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Received: 15 May. 2024
Revised: 05 Sep. 2024
Accepted: 06 Sep. 2024

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread worldwide since March 2020 and has become one of the public health concerns (1).

Mortality in patients with coronavirus disease 2019 (COVID-19) with underlying liver diseases compared with patients without it has been reported to be 12% versus 4%. Evidence showed that chronic liver diseases have an adverse effect on the clinical outcomes of patients with COVID-19. Conversely, the experience of the previous SARS epidemic has demonstrated that 60% of patients experienced various degrees of liver damage (2).

In the studies that assessed COVID-19 in liver transplantation (LT) recipients, the most common comorbidity was hypertension, and the most prevalent symptoms were fever (74.8%) and cough (70.3%). The majority of patients were receiving chronic immunosuppressive drugs. Almost 30% of patients received calcineurin inhibitor drugs, 26% in combination with mycophenolate, and 8% in combination with everolimus (3).

LT recipients are considered a high-risk group for COVID-19 since they receive life-long immunosuppressive therapy (3). On the other hand, the immune response may cause the dysregulation of CD4+ T cells and activation of CD8+ T cells and macrophages, which leads to a cytokine storm (the severe form of COVID-19) (4,5). Drug interactions between dexamethasone, calcineurin inhibitors (CNI), and hepatotoxicity associated with remdesivir and tocilizumab are well documented. Thus, there is a possibility of contradiction of the aforementioned drugs for the treatment of COVID-19 in LT recipients (6).

Studies claimed that the type of underlying liver disease leading to LT, such as hepatitis B and hepatocellular carcinoma (HCC), is related to the severity of COVID-19. In LT patients, the risk of infection with SARS-CoV-2 and the severity of the consequences are almost unknown (7,8).

Therefore, this study aimed to examine the factors that influence the relationship between LT and the consequences of COVID-19.

MATERIALS AND METHODS

In this cross-sectional study, all individuals with a history of LT who contracted COVID-19 through the Liver Transplantation Clinic, Imam Khomeini Hospital Complex, Tehran, Iran were recruited during the two years of the COVID-19 pandemic from March 2020 to March 2022. Imam Khomeini Hospital stands as a prominent center for LT in Iran. Patients who have undergone liver transplantation are mandated to attend the liver transplantation clinic every 3 months for scheduled follow-ups. During these sessions, a comprehensive review of their medical histories, including any occurrences of COVID-19, is conducted. Details about the management of this infection, whether in an inpatient or outpatient setting and the medications administered are meticulously examined and documented. The required data were extracted from patients' medical records and hospital databases, which included the patients' history, clinical examinations, and radiological findings. The characteristics and effective criteria in the relationship between the incidence and consequences of COVID-19 in LT recipients were investigated.

The clinical characteristics consist of underlying disease, liver disease type, type of received liver, clinical manifestations and received medications for COVID-19, laboratory parameters, degree of pulmonary involvement in imaging, and type of immunosuppressive drugs. Clinical manifestations of COVID-19 include fever, cough, shortness of breath, gastrointestinal symptoms, and being asymptomatic. In compiling the checklist of this section, World Health Organization (WHO) guidelines were used to determine the severity and prognosis of the disease. The COVID-19 was confirmed with a positive reverse transcription-polymerase chain reaction (RT-PCR) testtaken from the nasopharynx or nose.

The primary outcome assessed was severe COVID-19 defined as the need for mechanical ventilation, intensive care unit (ICU) admission, or death. This outcome was used in a past study to describe the clinical features of COVID-19 in China. Secondary outcomes were respiratory failure (partial arterial oxygen pressure <60 mmHg), need for mechanical ventilation, ICU admission, and liver allograft dysfunction. It is usually defined as an increase in bilirubin more than four times the baseline values, the international normalized ratio > 1.4, or an increase in liver enzymes up to 3 times the upper limit normal. The time interval between undergoing LT and the manifestation of COVID-19 was classified as "early" if it occurred within a period of less than one month and deemed "late" if the interval exceeded or equaled one month. Patients were considered cured of COVID-19 after hospital discharge or after two consecutive negative PCR results more than 48 hours apart, whichever occurred earlier.

The algorithm for LT during the COVID-19 pandemic was that patients had undergone surgery on the condition of having three negative PCR tests, the absence of any symptoms of COVID-19, and complying with 14 days of quarantine.

The patients eligible for this study were accurately informed of the purpose, methods, risks, benefits, and other research options. Then, they understood this information and related it to their clinical situation or interests, and eventually made a voluntary decision to participate in

this study. Informed consent was acquired from the participants. This study was conducted according to the Ethics Committee of the Hospital and had an ethics code. The analyses were conducted using IBM SPSS software version 22. In the determination of frequency, an assessment of normal distribution was conducted. For the qualitative variables, numerical representations, such as numbers and percentages, were employed, while quantitative variables were characterized using mean and standard deviation. In instances where the data exhibited non-normality, the median and the interquartile range index (IQR) were utilized. The comparison of mean values among qualitative subgroups for quantitative variables involved the application of the independent t test and Chi-square test. Non-parametric conditions were addressed using the Mann-Whitney test. Additionally, the analysis of variance (ANOVA) was applied to compare average values of quantitative variables across distinct independent groups. To examine the relationship between quantitative variables, bivariate analysis and Pearson's correlation coefficient were employed. For the exploration of associations between two qualitative variables, the crosstab command was utilized, with the Wilcoxon test applied in non-parametric scenarios. The analysis was univariate. These methodological approaches were selected to ensure a comprehensive and rigorous examination of the research data.

RESULTS

All files of liver recipient patients who visited the Liver Transplantation clinic and developed COVID-19 between March 2020 and March 2022 were reviewed. Among these files, 162 transplant recipients were identified. The baseline information of the studied patients is presented in table 1. Of the 162 studied patients, 154 (95.1%) underwent a single LT, while eight (4.9%) underwent two LTs. All the transplanted livers were obtained from cadavers.

Table 1. Basic demographic data of liver recipient patients with COVID-19

Variables	Mean±standard deviation
Sex (male)	99 (61.1%)*
Age at transplantation	47.51±13.51
BMI(kg/m^2)	25.33±3.51

*Number (percentage)

BMI: Body mass index

Table 2 demonstrates the underlying diseases that led to LT. The most common types were cryptogenic, primary sclerosing cholangitis (PSC), non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and hepatitis B, respectively.

Table 2. The type and frequency of underlying diseases led to LT

The underlying disease led to LT	Number (percentage)
Tyrosinemia	1 (0.6%)
Congenital hepatic fibrosis	1 (0.6%)
Hepatorenal syndrome	2 (1.2%)
Acute liver failure	7 (4.2%)
Acute on chronic liver injury	9 (5.4%)
Autoimmune hepatitis	14 (8.4%)
Alcoholic fatty liver	4 (2.4%)
Budd-Chiari syndrome	5 (3%)
Cryptogenic	32 (19.2%)
Hepatitis B	10 (6%)
HCC	3 (1.8%)
Hepatitis C	4 (2.4%)
NAFLD	16 (6.4%)
Neuroendocrine tumor	1 (0.6%)
Overlap syndrome	1 (0.6%)
PBC	3 (1.8%)
PSC	24 (14.4%)
Wilson's disease	3 (1.8%)
Re-transplantation in the past	4 (2.4%)
Autoimmune hepatitis and PSC	1 (0.6%)
Cryptogenic cirrhosis and HCC	1 (0.6%)
Hepatitis B and HCC	3 (1.8%)
Hepatitis B and hepatitis D	2 (1.2%)
Hepatitis B, hepatitis D, and HCC	1 (0.6%)
Hepatitis C and HCC	5 (3%)
PSC and cholangiocarcinoma	1 (0.6%)
PSC and HCC	1 (0.6%)
UC and PSC	2 (1.2%)

LT, liver transplantation; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; UC, ulcerative colitis

78.4% of patients had no underlying diseases in their medical history except the disease led to LT. The most common types were diabetes, hypertension, and dyslipidemia, respectively.

Table 3 demonstrates information on the immunosuppressive regimens received by the patients after LT and before COVID-19 infection.

Table 3. Prevalence of immunosuppressive regimens after LT and before COVID-19

Immunosuppressive regimen	Number (percentage)
Tacrolimus and mycophenolate mofetil	86 (51.6%)
Cyclosporine and mycophenolate mofetil	24 (14.4%)
CNI	21 (12.6%)
CNI and sirolimus	13 (7.8%)
CNI and everolimus	4 (2.4%)
Tacrolimus and cyclosporine	3 (1.8%)
Cyclosporine and sirolimus	3 (1.8%)
Sirolimus	2 (1.2%)
CNI, mycophenolate mofetil, and sirolimus	2 (1.2%)
CNI and azathioprine	1 (0.6%)
Mycophenolate mofetil and everolimus	1 (0.6%)
Cyclosporine	1 (0.6%)
Cyclosporine and azathioprine	1 (0.6%)

CNI, calcineurin inhibitor; LT, liver transplantation

The frequency of variables related to COVID-19 are shown in table 4. They include the time interval between undergoing LT and developing COVID-19, the severity of the COVID-19, the presence or absence of pulmonary involvement, the type of management (outpatient or inpatient) and medications received for COVID-19, and the outcome (survival or death). These data are presented in table 4.

Table 4. The frequency of variables related to COVID-19

Variable related to COVID-19	Subcategories	Number (percentage)
The time interval between undergoing LT and developing COVID-19	Early (<1 month)	38 (23.5%)
	Late (≥1 month)	124 (76.5%)
The severity of the COVID-19 infection	Low	108 (66.7%)
	High	54 (33.3%)
Type of management for COVID-19	Outpatient	111 (68.5%)
	Inpatient	51 (31.5%)
Pulmonary involvement	No	114 (70.4%)
	Yes	48 (29.6%)
Type of medications received for COVID-19	Supportive	112 (69.1%)
	Remdesivir	2 (1.2%)
	Remdesivir and steroid	48 (29.6%)
Outcome of COVID-19	Survival	123 (75.9%)
	Death	39 (24.1%)

LT, liver transplantation

The relationship between three outcome variables, including disease severity, death due to COVID-19, and liver enzyme disorders, with other variables was examined.

Disease severity of COVID-19

Regarding disease severity, no significant relationship was observed with age at the time of LT (P=0.52), body mass index (BMI) (P=0.98), sex (P=0.39), type of previous comorbidity (P=0.23), the time interval between infection and LT (P=0.11), pre-transplant MELD score (P=0.056), type of immunosuppressive regimen (P=0.61), and type of underlying disease leading to LT (P=0.9). However, a significant relationship was found between disease severity and the number of LTs (P=0.017), presence of pulmonary involvement (P<0.001), need for remdesivir and steroid treatment (P<0.001), and death (P<0.001).

Death Due to COVID-19

In patients who eventually died due to COVID-19, no significant relationship was observed between death and sex (P=0.45), BMI (P=0.29), pre-transplant MELD score (P=0.07), type of immunosuppressive regimen (P=0.65), previous underlying disease (P=0.34), and underlying disease leading to LT (P=0.42). However, a significant relationship was found between death and age at the time of LT (P=0.01), lung involvement (P<0.001), early infection (within one month of LT) with COVID-19 (P=0.01), and the need for hospitalization due to COVID-19 (P<0.001).

Liver Enzyme Disorders

Regarding liver enzyme disorders, there was no significant relationship between elevated alanine transferase levels (>40 U/L) and patient sex (P=0.32), age at the time of LT (P=0.62), BMI (P=0.49), number of received livers (P=1.00), pre-transplant MELD score (P=0.78), type

of immunosuppressive drug after LT (P=0.30), type of underlying disease leading to LT (P=0.12), and type of previous underlying disease (P=0.58). However, a significant relationship was found between elevated alanine transferase levels and early infection with COVID-19 (P<0.001), severe COVID-19 involvement (P=0.001), presence of pulmonary involvement (P=0.003), need for remdesivir and steroid treatment (P<0.001), and death due to COVID-19 (P=0.001).

Similarly, there was no significant relationship between elevated aspartate aminotransferase levels (>40 U/L) and patient sex (P=0.62), age at the time of LT (P=0.75), BMI (P=0.35), number of received livers (P=1.00), pre-transplant MELD score (P=0.13), type of immunosuppressive drug after LT (P=0.22), previous underlying disease (P=0.64), and type of underlying disease leading to LT (P=0.17). While significant associations were observed between elevated aspartate aminotransferase levels with early infection with COVID-19 (P<0.001), severe COVID-19 involvement (P=0.01), lung involvement (P=0.008), treatment with remdesivir and steroids (P=0.009), and death due to COVID-19 (P=0.008). These findings indicate a clear relationship between these variables.

Furthermore, in the analysis of patients who experienced an increase in total bilirubin levels exceeding 1.5 mg/dL, no significant relationships were found with the age of the patients at the time of LT (P=0.30), patients' BMI (P=0.79), number of received livers (P=0.21), type of immunosuppressive drug after LT (P=0.72), underlying disease leading to LT (P=0.06), and previous underlying disease (P=0.11). However, a significant relationship was observed between an increase in total bilirubin levels exceeding 1.5 mg/dL and female sex (P=0.02), early infection with COVID-19 (P<0.001), severe COVID-19 involvement (P=0.01), pulmonary involvement (P=0.002), pre-transplant MELD score (P=0.01), treatment with remdesivir and steroids (P=0.004), and death due to COVID-19 (P=0.01).

DISCUSSION

This study investigated the factors influencing the initial and final events of COVID-19 infection in patients receiving LT. Of the patients included, 61.1% were male and 38.9% were female. In a 2021 cohort study by Colmenero et al. in Spain, 71.1% of LT patients with COVID-19 were men (3).

The most commonly administered immunosuppressive regimen in this study was the combination of tacrolimus and mycophenolate mofetil. These two drugs have been frequently used among patients receiving LT, as indicated by other similar studies (3,9-13).

Among the patients included in this study, 23.5% developed COVID-19 within one month of LT, while the remaining cases were infected later, with an interval of more than one month. In the study conducted by Colmenero et al., 13.5% of patients developed COVID-19 within 1 year after LT (3). Furthermore, in a European cohort study by Becchetti et al. in 2020 on COVID-19 in patients receiving LT, 19% of patients were infected within 1 month of LT, and the average time from LT to COVID-19 was approximately 6 years (11).

Of the patients with COVID-19 in this study, 31.5% required hospital admission, while 68.5% were managed as outpatients. In a 2019 study by Mansoor et al. in the United States, 40% of LT patients with COVID-19 required hospitalization (9). In contrast, the study by Becchetti et al. reported that 72% of patients receiving LT required hospital admission (11). One possible explanation for this difference could be the lower prevalence of comorbidities among patients in our study, which was observed in 78.4% of cases. In Becchetti et al. study, 71.2% of patients had at least one comorbidity, such as cardiovascular, diabetes, or pulmonary disease. This finding contradicts the results of a 2020 systematic review study by Moris et al. on kidney transplant patients with COVID-19, where 86.1% of patients required hospital admission for treatment (14).

According to the definitions used in this study, 33.3% of patients were diagnosed with a severe form of COVID-19. In the study conducted by Colmenero et al., utilizing similar criteria for disease severity, 31.5% of patients were diagnosed with a severe form of the disease (3). Another study conducted by Eren-Kutsoylu et al. in 2023 on the same topic reported that 31.5% of patients were diagnosed with a severe form of the disease (15).

In this study, the final consequences of COVID-19 were examined from three perspectives: disease severity, mortality, and liver enzyme disorders. Regarding disease severity, no significant relationships were found between patients' sex, BMI, comorbidity type, MELD score before LT, type of immunosuppressive regimen received, and the type of underlying disease leading to LT. Although comorbidity is generally considered a risk factor for the incidence and severity of COVID-19, our study did not find a significant relationship between comorbidity and disease severity. This may be attributed to the fact that 78.4% of the patients included in the study had no clinical history of diseases other than liver disease. Therefore, this finding cannot be generalized to other studies.

While the MELD score in patients with chronic liver disease is generally considered a risk factor for the severity and mortality of COVID-19, a systematic review conducted by Choudhary et al. in 2021 demonstrated that the MELD score before LT has no impact on the severity of

morbidity and mortality after LT (16). Similarly, the type of immunosuppressive regimen received and the underlying disease leading to LT did not affect the severity of the disease, which is consistent with findings from other similar studies (3,10). The number of LT recipients had a direct relationship with the severity of COVID-19. However, due to the small sample size, this finding is unreliable and cannot be generalized. The amount and duration of exposure to immunosuppressive drugs may explain this finding despite the limited sample size. Patients who experienced pulmonary involvement and required the use of remdesivir and/or corticosteroid drugs during treatment were significantly associated with the severe form of the disease. Additionally, a higher proportion of patients with severe COVID-19 outcomes died compared with those with non-severe forms. This finding is consistent with previous studies conducted on both transplant and non-transplant patients with COVID-19 (1-3,17-20). Regarding patient mortality in our study, 24.1% of patients died at the end of treatment. In the study conducted by Colmenero et al., the mortality rate was 18% (3), while in the US cohort study by Webb et al., it was 8% (9). The study by Becchetti et al. reported a mortality rate of 12%, and the ELITA/ELTR study reported a rate of 22% (11). The variation in mortality rates among these studies may be attributed to differences in sample sizes. In all the aforementioned studies, age has been considered an influential factor in the mortality of patients receiving LT, with most studies identifying 60 years as the cutoff age associated with increased mortality. Our study also found a significant relationship between age at the time of LT and patient age with the mortality rate.

Furthermore, the presence of pulmonary involvement, the need for remdesivir and corticosteroid treatment during hospital admission, and the requirement for hospital admission were significantly associated with mortality. These findings are consistent with other studies conducted in the field, both among transplant patients (3,9-12) and non-transplant patients (17,18). An important finding in our study was the significant relationship between early COVID-19 and mortality. This finding contradicts the study by Becchetti et al. in 2020, where the severity of symptoms and mortality in patients receiving LT were lower in the first year after LT (11). The higher mortality in patients receiving LT within the first month in our study may be attributed to the proximity of COVID-19 and surgery, which are both major stress factors. A study by Haffner et al. in 2021 considered COVID-19 as an independent risk factor for mortality (not just severity) in surgical patients (21). Regarding liver enzyme disorders in our study patients, elevated levels of alanine transferase and aspartate aminotransferase above 40 U/L, as well as an increase in total bilirubin above 1.5 mg/dL, were significantly associated with pulmonary involvement, death, and disease severity requiring remdesivir and corticosteroids. A systematic review and meta-analysis by Malik et al. in 2021, which included 32 studies and a total sample size of 10,491patients with COVID-19, identified elevated levels of alanine aminotransferase as a laboratory marker associated with poor prognosis in infected patients, consistent with our findings (22).

Furthermore, in patients infected early, the level of liver enzyme disorders and their increase was higher compared with the late-onset group. A study by Fedoravicious and Charlton in 2016 on patients receiving LT considered viral infections themselves as a factor in elevated liver enzymes. However, contrary to our study, this study found that liver enzyme disorders were higher in viral infections occurring one to six months after LT compared with other times (23). Nevertheless, this finding can be interpreted differently. Since the mortality rate is higher in the early-onset COVID-19 group compared with the late-onset group, and the levels of these enzymes are higher in severe cases associated with mortality, the increase in these enzymes may be more pronounced in the early-onset group compared with the late-onset group.

Regarding the limitations of our study implementation, there were challenges in accessing patients with critical COVID-19 conditions and recording their information. Additionally, while our study had the largest sample size compared with the mentioned studies, a more accurate interpretation of the findings would require a systematic review and meta-analysis incorporating data from various studies.

CONCLUSION

In conclusion, advanced age, pulmonary involvement, dependence on corticosteroid and remdesivir treatment, the number of LTs, and elevated liver enzyme levels were significant risk factors associated with severe COVID-19 and mortality. There was no significant relationship between the type of pre-transplant immunosuppressive regimen, underlying disease type, and the cause of LT with disease severity and mortality.

ACKNOWLEDGMENTS

We thank the study participants.

CONFLICT OF INTERESTS

The authors declare no conflict of interest related to this work.

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