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Case Control Study

Clinical outcomes of coronavirus disease 2019 in liver transplant recipients

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Abstract

BACKGROUND

Liver transplant patients are at higher risk of infection due to immunosuppression. Whether liver transplant recipients are also more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and will have worse outcomes than the general population if they develop coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 is a topic of ongoing studies, including ours.

AIM

To assess the clinical outcomes of COVID-19 in liver transplant recipients.

METHODS

This was a case-control study, with a database search performed (at the study site) from March 1, 2020 through February 28, 2021. Patients 18 years or older who tested positive for SARS-CoV-2 *via* polymerase chain reaction (PCR) were included in the study. Patients with infection other than pneumonia at the time of admission were excluded. After selection, patients who had been the recipient of liver transplant were considered cases and those without as controls. After being matched by age, sex, and obesity, two controls were randomly selected for each case. Death and hospitalization due to COVID-19 infection were the primary outcomes. Secondary outcomes were pertinent

only to patients who were hospitalized, and they included duration of hospital stay, need for supplemental oxygen, presence of at least one type of end-organ damage, effects on liver enzymes, incidence of acute liver failure, effect on d-dimer levels, and incidence of venous thromboembolism (VTE). Chi-square or Fisher's exact test was used to compare all primary and secondary outcomes with the exception of duration of hospital stay and d-dimer levels, which were compared using the Wilcoxon signed-rank test. Alpha criterion was set at 0.05. Logistic regression was performed for each primary outcome (as the dependent variable). Statistical analyses were performed using R software.

RESULTS

Of the 470 Liver transplant recipients who were tested for COVID-19 *via* the PCR test, 39 patients tested positive (8.3%). There was no significant difference between cases and controls regarding death (odds ratio [OR]: 2.04, 95% confidence interval [CI]: 0.14–29.17; $P = 0.60$) and hospitalization rates (OR: 1.38, 95%CI: 0.59–3.24; $P = 0.46$). There also was no significant difference between cases and controls with respect to all secondary outcomes. Among all patients who had elevated liver enzymes, their levels were either normalized, improving, or remained stable at the time of discharge. No patient developed acute liver failure. Of the 31 hospitalized patients, 27 received a prophylactic anticoagulation dose and no patient developed VTE in either group. Among cases who were hospitalized, immunosuppression was decreased in 5 patients and there was no change in immunosuppression among the remaining 7 patients. One patient died in each of these two subgroups. Logistic regression analysis was done, but all of the models had poor model predictions as well as insignificant predictors (independent variables). Therefore, they could not be used for either prediction or inference.

CONCLUSION

Clinical outcomes of COVID-19 in liver transplant recipients are not different than those without transplantation.COVID-19 should not impact timely health care access and immunosuppression continuation among these patients.

INTRODUCTION

According to the John Hopkins University Coronavirus Resource Center, more than 480 million people have contracted coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and more than 6.1 million people have died worldwide from it as of the writing of this manuscript[1]. In the United States alone, more than 79 million people have contracted COVID-19 and more than 900,000 people have died from it[1]. This reflects the gravity of the situation.

COVID-19 primarily affects lungs, but evidence suggests the potential involvement and complications of other organ systems as well including cardiovascular, hematological, and neurological systems[2-5]. Liver injury, as demonstrated by elevated liver enzymes, has also been reported in many observational studies[6, 7].

Patients with solid organ transplant are at higher risk of infection due to immunosuppression[8]. Whether SARS-CoV-2 causes more frequent infections, more hospitalizations, and is associated with worse outcomes among solid organ transplant patients have been the subject of many studies. In their systematic review of 215 studies, Raja *et al*[9] reported that the incidence of hospitalization was higher among patients with solid organ transplantation compared to patients with no transplant. Pooled incidence of all-cause mortality was 18.6% for all solid organ transplant recipients combined and 11.8% for liver transplant recipients in their study[9]; however, mortality comparison with non-transplant patients was not provided. Kulkarni *et al*[10] focused only on liver transplant recipients with COVID-19 in their systematic review of 18 studies and reported that the cumulative incidence of all-cause mortality was 17.4% among patients with liver transplant who had COVID-19. The authors also provided a comparison and reported that there was no difference in mortality between non-

transplant and liver transplant patients after being diagnosed with COVID-19, despite a change in immunosuppression in 55.9% of the liver transplant patients[10]. The fact that all-cause mortality of COVID-19 is not different among liver transplant recipients compared to non-transplant patients, has been reported by Jayant *et al*[11] as well as in their systematic review of 12 studies. Colmenero *et al*[12] also reported a higher risk of COVID-19 among liver transplant recipients, but surprisingly, mortality was lower for liver transplant recipients in their prospective study. Complete immunosuppression withdrawal also showed no benefit in their study[12].

The data on other outcomes of COVID-19 among liver transplant recipients besides hospitalization and mortality, such as duration of hospital stay and acute liver failure, are limited and heterogeneous. Since liver transplant recipients require specialized care and timely access to health care, we explored additional outcomes of COVID-19 among these patients besides mortality and hospitalization rates.

MATERIALS AND METHODS

Study design

This was a case-control study. After approval from the institutional review board, a list of patients was obtained with the help of the Clinical Informatics Department from the database of the study site from March 1, 2020 through February 28, 2021, using the selection criteria given below.

Selection criteria

Inclusion criteria: Adult patients (age 18 years or above) who tested positive for SARS-CoV-2 *via* polymerase chain reaction (PCR).

Exclusion criteria: With the exception of bacterial pneumonia (which can be a direct complication of COVID-19 itself), patients with definitive evidence of any other infection, such as positive blood culture or positive urine analysis along with positive urine culture, were excluded (as the presence of another infection besides COVID-19

can also independently increase the risk of adverse outcomes and can be a confounding factor). Among patients who met the above inclusion and exclusion criteria, patients who had been the recipient of liver transplant were considered cases and those without liver transplant were considered controls.

Outcomes

Death and hospitalization due to COVID-19 were the primary outcomes. Secondary outcomes were pertinent only to patients who were hospitalized and included duration of hospital stay (in days), need for supplemental oxygen, presence of at least one type of end-organ damage (*e.g.,* acute kidney injury or elevated troponins), effect on liver enzymes and incidence of acute liver failure due to COVID-19, effect on d-dimers and incidence of venous thromboembolism (VTE).

Data analyses

Cases and controls were first matched by age, sex, and obesity. After controls were identified and matched with cases based on the aforementioned three variables, two controls were selected for each case (frequency matching) using random sampling. Cases and controls were compared with each other for primary and secondary outcomes. The

Chi-square or Fisher's exact test was used to compare all primary and secondary outcomes with the exception of duration of hospital stay and d-dimer levels, which were compared between cases and controls using the Wilcoxon signed-rank test. Alpha criterion was set at 0.05. Logistic regression was performed for each primary outcome (as the dependent variable) as well. All statistical analyses were performed using R software.

RESULTS

Of the 470 Liver transplant recipients who were tested for COVID-19 *via* PCR, 39 patients tested positive (8.3%), of whom 31 were symptomatic and 8 were

asymptomatic. The general characteristics of cases and controls are given in Table 1. The characteristics of cases, pertinent to their liver transplantation, are given in Table 2.

No significant difference was found in death or rate of hospitalization due to COVID-19 between those who had liver transplantation (cases) and those who did not (controls), as detailed in Tables 3 and 4. A total of 31 patients were hospitalized (cases = 12, controls = 19). The mean duration of hospital stay for cases and controls was 8.25 ± 6.92 d and 9.84 ± 17.33 d, respectively. There was no significant difference in duration of hospital stay between the two groups (P = 0.412).

In total, 8 of 12 cases (66.7%) and 14 of 19 controls (73.7 %) either had new supplemental oxygen requirement or an increase from baseline supplemental oxygen needs (if they were already on supplemental oxygen at baseline). There was no significant difference between cases and controls in terms of increase in oxygen requirements (odds ratio [OR]: 0.722, 95% confidence interval [CI]: 0.11-4.78; P = 0.70). Of the remaining 27 patients (4 patients died of COVID-19), only 5 had higher than baseline oxygen requirement at the time of discharge (cases = 2, controls = 3). Except for 3 patients (cases = 2 cases, controls = 1), all patients who had an increase in oxygen requirement from its baseline received both dexamethasone 6 mg daily and intravenous remdesivir. In all, 6 of 12 cases (50%) and 7 of 19 controls (36.8%) had at least one type of end-organ damage. There was no significant difference between the two groups in terms of end-organ damage (OR: 1.71, 95%CI: 0.4-7.43; P = 0.47).

No liver enzyme data were available for 1 case and 4 controls. Analyses of the remaining 26 hospitalized patients (cases = 11, controls = 15) revealed that aspartate aminotransferase (AST) was elevated among 3 cases (27.27%) and 10 controls (66.66%), and this difference was not statistically significant (OR: 0.19, 95%CI: 0.03-1.03; P = 0.05). Alanine aminotransferase (ALT) enzyme elevation rate was also surprisingly low among cases, but there was no significant difference between the two groups (OR: 0.27, 95%CI: 0.021–2.0; P = 0.22). Only 1 patient had AST and ALT greater than 3 × the upper limit of normal (ULN). Among all patients who had elevated AST or ALT, their levels

either normalized, were improving, or remained stable at the time of discharge. No patient developed acute liver failure.

No data were available on d-dimer level for 1 case and 1 control. For the remaining cases (n = 11) and controls (n = 18), the mean values of the first d-dimer level during hospitalization were 1800.7 ng/mL and 915 ng/mL, respectively. This difference in d-dimer levels was not statistically significant between the two groups (P = 0.47). One patient among cases did not receive anti-coagulation due to thrombocytopenia. One patient among controls was already on warfarin for history of atrial fibrillation. All other remaining patients (cases = 10, controls = 17) received a prophylactic dose of either subcutaneous unfractionated heparin (n = 4) or enoxaparin (n = 23). No patient developed VTE in either group. Among the cases who were hospitalized (n = 12), immunosuppression was decreased in 5 patients and did not change among the remaining 7 patients. One patient died in each of these two subgroups. Logistic regression analyses were conducted, but all of the models gave poor predictions as well as insignificant predictors (independent variables). Therefore, they could not be used for either prediction or inference.

DISCUSSION

Our study did not show a significant difference in death or hospitalization rate due to COVID-19 between patients who had liver transplantation and those who did not. Our study also did not find a difference between these two groups in terms of duration of hospital stay, need for supplemental oxygen, presence of at least one type of end-organ damage, effect on liver enzymes, and effect on d-dimer levels. Although case count was low, reducing immunosuppression in a few patients did not have obvious effects on mortality and need for supplemental oxygen.

Co-morbidities such as obesity, diabetes, cardiovascular and chronic pulmonary diseases have been associated with worse outcomes among patients with COVID-19[13,14]. However, surprisingly, liver transplant status did not increase the risk of mortality for these patients in our study, and this finding is in line with the results of

recently published systematic reviews[11,15]. Although higher hospitalization rate has been reported among solid organ transplant patients with COVID-19, our study did not show any such difference[9].

There is no reliable comparison available to date for duration of hospital stay for COVID-19 between patients who are or are not liver transplant recipients. On average, patients in each group spent more than 1 wk in the hospital according to our study. Also, data on the need for supplemental oxygen among liver transplant recipients with COVID-19 are limited[16]. There is no comparison available to date for oxygen requirement among COVID-19 patients who have been liver transplant recipients' compared to those who are not. Most patients in both groups required supplemental oxygen in our study, but there was no statistically significant difference between the two groups in terms of oxygen requirements and only 5 of 27 discharged patients (cases = 2, controls = 3) required supplemental oxygen at the time of discharge.

Rabiee *et al*[17] reported moderate acute liver injury (ALT 2-5 × ULN) to be 22.2% (n = 18) and severe acute liver injury (ALT > 5 × ULN) to be 12.3% (n = 10) among liver transplant recipients who were diagnosed with COVID-19. Acute liver injury was lower among liver transplant recipients compared to patients with other chronic liver disease and COVID-19 according to their study[17]. Although we also noted overall lower values of ALT and AST among patients who had liver transplant compared to those who did not, this difference was not statistically significant in our study.

No reliable comparison exists to date for d-dimer levels and incidence of VTE in COVID-19 between patients who are and are not liver transplant recipients. D-dimer levels were higher in hospitalized liver transplant recipients compared to patients without any transplant; however, this difference was not statistically significant in our study. Most patients received prophylactic anti-coagulation against VTE, and no patient was diagnosed with VTE during their hospitalization.

In summary, our study shows that the clinical outcomes of COVID-19 between patients with and without liver transplant are not different. Important limitations of our study include the retrospective nature of the study, relatively small sample size, and the

fact that it was a single-center study. Also, given the retrospective nature of the study, the severity of the comorbidities among cases and controls could not be estimated.

CONCLUSION

Clinical outcomes of COVID-19 do not differ among patients with and without liver transplantation. Also, decreasing immunosuppression in limited liver transplant patients did not improve morbidity or mortality. Precautions, vaccination, and appropriate testing should be exercised but otherwise, the ongoing COVID-19 pandemic should not change how liver transplant patients are cared for, such as timely access to health care and continuation of immunosuppression.

ARTICLE HIGHLIGHTS

Research background

Liver transplant patients are at higher risk of infection due to immunosuppression. Whether liver transplant recipients are also more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and will have worse outcomes than the general population if they develop coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 is a topic of ongoing studies, including ours.

Research motivation

Liver transplant recipients require specialized care and timely access to health care. However, the data on outcomes of COVID-19 among liver transplant recipients besides hospitalization and mortality is limited. This led to our interest to explore additional outcomes of COVID-19 among liver transplant recipients.

Research objectives

The objective of the study was to assess clinical outcomes of COVID-19 in liver transplant recipients. Death and hospitalization due to COVID-19 were the primary outcomes. Secondary outcomes were pertinent only to patients who were hospitalized,

and they included duration of hospital stay, need for supplemental oxygen, presence of at least one type of end-organ damage, effects on liver enzymes, incidence of acute liver failure, effect on d-dimer levels, and incidence of venous thromboembolism.

Research methods

This was a case-control study. Patients 18 years or older who tested positive for SARS-CoV-2 *via* polymerase chain reaction were included in the study. Patients with infection other than pneumonia at the time of admission were excluded. Patients who had been the recipient of liver transplant were considered cases and those without as controls. Chi-square or Fisher's exact test was used to compare all primary and secondary outcomes with the exception of duration of hospital stay and d-dimer levels, which were compared using the Wilcoxon signed-rank test. Alpha criterion was set at 0.05. Statistical analyses were performed using R software.

Research results

There was no significant difference between cases and controls regarding death and hospitalization rates. There also was no significant difference between cases and controls with respect to all secondary outcomes.

Research conclusions

Clinical outcomes of COVID-19 in liver transplant recipients are not different than those without transplantation. COVID-19 should not impact timely health care access and immunosuppression continuation among these patients.

Research perspectives

Besides hospitalization and mortality, data on additional clinical outcomes of COVID-19 among liver transplant recipients is limited. Additional studies are needed to explore the full impact of COVID-19 among patients who have been the recipient of liver transplant.

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