

Impact of COVID-19 on liver transplant recipients during the first pandemic wave, in a tertiary hospital, in Northeastern Brazil

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ABSTRACT

Worldwide, transplant programs have suffered a setback during the coronavirus disease 2019 (COVID-19) pandemic and most have temporarily suspended their transplant activities. We identified 36 liver transplant patients who tested positive for COVID-19. The cases were confirmed by the nucleic acid test (RT-PCR). Epidemiological, demographic, clinical, laboratory, management and outcome data were obtained from the patients' medical records. Fourteen patients (38.9%) required admission to the Intensive Care Unit and/or invasive ventilatory support (severe cases). The mean age of these severe cases was 63.8 years. Regarding the time since the transplant, 71.4% (10/14 patients) had undergone the procedure less than one year before. The immunosuppressive therapy was reduced in patients who required Intensive Care Unit. A total of 12 cases (12/14, 85.7%) required invasive ventilatory support. Eight cases (8/14, 57.1%) required renal replacement therapy. In this group of patients, nine died (64.3%). In turn, 22 patients had mild to moderate symptoms of COVID-19, not requiring invasive ventilatory support or admission to the Intensive Care Unit. The mean age in these patients was 56.5 years and comorbidities were present in 15 (68.2%) of the cases. In this group, only five patients (5/22, 22.7%) required hospitalization due to complications and there were no deaths. This report describes the results of COVID-19 infection in a very specific population, suggesting that liver transplant patients have a significant higher risk of progressing to severe COVID-19, with a mortality rate among critically-ill patients above that of the general population.

KEYWORDS: Coronavirus infections. Liver transplantation. COVID-19.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has revolutionized healthcare systems around the world and led to an inevitable decline in liver transplant activity. This severe decline in the transplant activity was due to concerns on potentially increased susceptibility and worse outcomes of COVID-19 in transplant recipients^{1,2}. Thus, information characterizing COVID-19 infection in transplant recipients is of great relevance for the understanding of the disease behavior in patients with this profile.

MATERIALS AND METHODS

The Liver Transplant Service at the Hospital Geral de Fortaleza, Ceara State,

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Received: 24 May 2021

Accepted: 9 December 2021

Brazil, performs the outpatient follow-up of 450 patients. For this retrospective, single-center study, we recruited patients from March 2020 to December 2020. We identified 36 liver transplant patients who tested positive for COVID-19. The cases were confirmed by the nucleic acid test (RT-PCR). Moreover, patients who required admission to the Intensive Care Unit and/or invasive ventilatory support were considered to have a severe form of COVID-19. In turn, patients who did not require invasive ventilatory support or admission to the Intensive Care Unit were considered to have mild to moderate COVID-19.

Epidemiological, demographic, clinical, laboratory, management and outcome data were obtained from the patients' medical records as described in [Tables 1](#) and [2](#). The project was approved by the Research Ethics Committee of Hospital Geral de Fortaleza, under the N° 56156316.5.0000.5040.

RESULTS

A total of 36 patients who tested positive for COVID-19 were identified and the cases were confirmed by the

Table 1 - Clinical characteristics of 36 liver transplant recipients diagnosed with COVID-19 during the first pandemic wave and divided into two groups according to the severity of COVID-19, in Northeastern Brazil.

VARIABLE	Values (patients meeting the severity criteria)	Values (patients not meeting the severity criteria)
Sociodemographic data		
Number	14	22
Mean age	63.8	56.5
Need for hospitalization	14/14 (100%)	5/22 (22.7%)
Time since transplant <1 year	10/14 (71.4%)	9/22 (41%)
Time since transplant >1 year	4/14 (28.6%)	13/22 (59%)
Comorbidities	14/14 (100%)	15/22 (68.2%)
Etiology of the transplant		
Alcohol cirrhosis	6/14 (42.8%)	7/22 (31.8%)
Cirrhosis due to primary sclerosis cholangitis	1/14 (7.1%)	2/22 (9.1%)
Hepatitis B virus cirrhosis	2/14 (14.3%)	3/22 (13.6%)
Nonalcoholic fatty liver disease	4/14 (28.6%)	5/22 (22.7%)
Hepatocellular carcinoma	1/14 (7.1%)	3/22 (13.6%)
Hepatitis C virus cirrhosis	**	2/22 (9.1%)
Signs and symptoms		
Fever	13/14 (92.8%)	15/22 (68.2%)
Dyspnea	13/14 (92.8%)	5/22 (22.7%)
Cough	9/14 (64.3%)	10/22 (45.4%)
Diarrhea	4/14 (28.6%)	10/22 (45.4%)
Myalgia	7/14 (50%)	16/22 (72.7%)
Odynophagia	8/14 (57.1%)	15/22 (68.2%)
Therapy		
Antibiotics	14/14 (100%)	7/17 (41.2%)
Corticosteroids	12/14 (85.7%)	7/22 (41.2%)
Reduction of immunosuppression	14/14 (100%)	5/22 (22.7%)
Outcome		
Monitored through telemedicine	0/14 (0%)	17/22 (77.3%)
Deaths by group	9/14 (64.2%)	0/22 (0%)
Discharged from hospital	3/14 (21.4%)	5/22 (22.7%)
Renal replacement therapy	8/14 (57.1%)	2/22 (9.1%)
Mechanical ventilation and/or ICU	14/14 (100%)	0/22 (0%)
Overall Mortality	9/36 (25%)	

Table 2 - Laboratory characteristics of 36 liver transplant patients diagnosed with COVID-19 during the first pandemic wave and divided into two groups according to the severity of COVID-19, in Northeastern Brazil.

VARIABLE	Values (patients meeting the severity criteria)	Values (patients not meeting the severity criteria)
Laboratory values		
<i>D-dimer</i>		
Patients with levels > 0.5 µg/mL and < 3 µg/mL	6/14 (42.8%)	5/22 (22.7%)
Patients with levels > 3 µg/mL	8/14 (58.2%)	4/22 (18.9%)
<i>APTT</i>		
Patients with levels > 2 s	9/14 (64.3%)	6/22 (27.3%)
<i>Lymphopenia</i>		
Patients with levels < 1,000 per mm ³	13/14 (92.8%)	11/22 (50%)
<i>C-reactive protein</i>		
Patients with levels > 5 mg/L	14/14 (100%)	15/22 (68.2%)
<i>Ferritin</i>		
Patients with levels > 900 ng/dL	13/14 (92.8%)	8/22 (36.4%)
<i>Fibrinogen</i>		
Patients with levels > 900 ng/dL	12/14 (85.7%)	9/22 (41%)
<i>Leukocytes</i>		
Patients with levels > 10,000 mm ³	13/14 (92.8%)	11/22 (50%)
<i>Platelets</i>		
Patients with levels < 150,000	10/14 (71.4%)	15/22 (68.2%)

nucleic acid test (RT-PCR). Nineteen patients (19/36, 52.8%) required hospitalization. The other 17 patients were followed-up through telemedicine consultations and received a conservative treatment.

In the present study, 14 (14/36, 38.9%) patients required admission to the Intensive Care Unit and/or invasive ventilatory support and were considered to have a severe evolution of COVID-19. The mean age of severe cases was 63.8 years. Regarding the time since the transplant, 10 out of 14 patients (71.4%) had undergone the procedure less than one year before.

The most frequently found comorbidities in severe cases were hypertension (10 cases, 71.4%), diabetes mellitus (12 cases, 85.7%) and chronic kidney disease (3 cases, 21.4%). The most common reported symptom was fever (13 cases, 92.8%), cough (9 cases, 64.3%) and dyspnea (13 cases, 92.8%). All patients who met the severity criteria had more than 25% of pulmonary involvement with ground-glass opacities in the chest computed tomography.

A total of 14 patients required admission to the Intensive Care Unit and 12 of them (85.7%) required invasive ventilatory support. The prone position was indicated in nine patients (64.2%) with an oxygenation index lower than 150. Eight cases (57.1%) required renal replacement therapy. In this group of patients, nine died (64.2%): four patients due to refractory hypoxemia, two patients due

to embolic events and three patients due to septic shock secondary to bacterial or fungal infections.

Inflammatory markers were measured in all 14 critically-ill COVID-19 patients, as described in Table 2, and a significant increase in these markers is present in more than half of the cases. In addition, lymphopenia was observed in 13 of the 14 patients (92.8%).

In the study, immunosuppressive therapy was reduced in the majority of patients, especially in those who needed hospitalization. Moreover, dexamethasone or methylprednisolone was administered to twelve patients (12/14, 85.7%).

In turn, 22 (22/36, 61.1%) patients had mild to moderate COVID-19 symptoms, and they did not require invasive ventilatory support or admission to the Intensive Care Unit. The mean age of these patients was 56.5 years and comorbidities were present in 15 of 22 patients or 68.2% of them. In this group, only five patients (22.7%) required hospitalization due to complications associated with COVID-19, such as bacterial pneumonia and there were no deaths.

DISCUSSION

After transplant, patients routinely receive higher doses of immunosuppression immediately after the procedure.

According to the protocol of the study hospital, 0.1 mg/kg/day of tacrolimus is used to maintain the immunosuppressant level between 4-7 ng/mL in the first three months and 3-5 ng/mL after the 5th month onwards, in association with mycophenolate mofetil and prednisone, with the latter being usually administered in the first three months. Reducing the dose of immunosuppressants during COVID-19 infection has been widely discussed, as there is a possible association between a deficient viral control and higher levels of these drugs, contributing to a more unfavorable evolution³. The retrospective analysis of different series during the first COVID-19 pandemic wave showed that immunosuppression was modified in nearly half of the cases, most frequently in patients with moderate and severe COVID-19, but immunosuppression was rarely discontinued^{4,5}. The American Association for the Study of Liver Disease recommends reducing the overall level of immunosuppression and considering reducing but not interrupting daily calcineurin inhibitor dosing, especially in the context of lymphopenia, fever, or worsening pulmonary status attributed to COVID-19³. Similar to other studies^{3,6,7}, immunosuppressive therapy was reduced in patients who required hospitalization, but immunosuppression was not interrupted. The impact of this approach is not clear. There is concern that immunosuppression may be associated with poorer virological control, leading to more severe COVID-19. Conversely, reducing immunosuppression may lead to acute rejection of the organ and cause an immune reconstitution-like reaction with a paradoxical worsening of disease⁸. It was interesting to notice that 71% of hospitalized patients were within one year of transplant, which suggests a possible contribution of immunosuppression to the severity of COVID-19.

Patients with severe disease were also more likely to have comorbidities. These results are in line with those of studies that found a greater severity in patients older than 60 years with comorbidities^{9,10}. In addition, diabetes mellitus, present in a substantial portion of the studied sample, showed a strong association with worse clinical outcomes in previous studies¹¹.

In the present study, the most common symptoms were fever, cough and dyspnea, similar to the ones reported in the general population¹². Immunosuppressed patients commonly present with atypical or attenuated signs and symptoms of infection, often leading to late presentations or missed diagnoses, potentially leading to worse overall outcomes.

Furthermore, compared with the general population and other studies that evaluated patients undergoing solid organ transplantation, a significantly higher mortality rate can be observed, which may be a consequence of the complexity of the patients treated in our service, as well as

the presence of variables known to be associated with an unfavorable outcome, such as comorbidities and advanced age. Moreover, COVID-19 is rapidly spreading around the world with devastating consequences for patients, health care workers, health systems and economies. The health system overload in times of pandemic may have contributed to the occurrence of adverse effects. Kates *et al.*¹³ conducted a multi-center study with patients in the postoperative period of solid organ transplants who had COVID-19. About 30% of the patients required invasive ventilatory support and had a mortality rate of 20.5%, which was mainly related to the presence of comorbidities and the patients' age. In addition, Huang *et al.*¹² observed a mortality rate in the general population of 38% in patients who required hospitalization in Intensive Care Units.

SARS-CoV-2 has tropism for the respiratory mucosa, but it is also able to infect other organs and systems leading to a cytokine storm that triggers a series of systemic immune and inflammatory responses¹⁴. Inflammatory markers were measured in all 14 critically-ill patients and a significant increase in these markers was present in more than half of the cases.

Although there is no specific treatment for COVID-19, the use of corticosteroids reduces the mortality in patients with COVID-19 who required respiratory support¹⁵. A study published by the RECOVERY group showed that 6 mg/day of dexamethasone for 10 days resulted in a lower mortality rate in 28 days, in patients who required oxygen therapy¹⁵. Thus, corticosteroid therapy was started for the treatment of severe cases, especially those in phase 2 (inflammatory stage) of the disease, with an average disease duration of more than seven days. In the study, dexamethasone or methylprednisolone was administered to 12 patients (12/14, 85.7%).

Several medications have been studied in the treatment of SARS-CoV-2 infection, such as remdesivir, tocilizumab, COVID-19 convalescent plasma, and immunoglobulin, among others. Some of these medications are already used in private hospitals/clinics, but are still unavailable in the Brazilian public health system.

The 22 patients with mild to moderate COVID-19 symptoms were monitored through telemedicine consultations and the symptoms control was performed using symptomatic medications¹⁶. There were no deaths among the patients with mild to moderate symptoms. Among patients who did not require intensive care, a Chinese prospective study showed a hospitalization rate of 21% for cases with mild to moderate symptoms¹², similar to the results of the present study. The same study showed a mortality rate of 4% in patients with this profile¹². In the present study, mild to moderate cases evolved to cure. Therefore, telemedicine follow-up resulted in effective patients' monitoring, with the prompt

identification of cases requiring hospitalization, making an early intervention possible.

CONCLUSION

There are some study limitations, due to the observational nature and the small number of cases described in the initial phase of the pandemic. However, in addition to helping the improvement of medical care of transplant patients in the subsequent phases of the pandemic in our service, this initial report describes the results of COVID-19 infection in a very specific population, thus suggesting that liver transplant patients have a significant higher risk of progressing to severe disease, with a mortality rate in critically-ill patients above that observed in the general population. Therefore, these results highlight the challenges and issues associated with organ transplants during the COVID-19 pandemic, providing data to assist in the early management of these patients. Moreover, the study highlights the importance of telemedicine and the early screening of liver transplant patients as a follow-up method, allowing an early diagnosis. The transplant centers should be able to readjust daily procedures to the evolution of the COVID-19 pandemic, and medical care during the pandemic must be stepped up.

CONFLICT OF INTERESTS

The authors declare they have no conflict of interests.

FUNDING

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

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