




CASE REPORT

Liver transplant recipients infected with SARS-CoV-2 in the early postoperative period: Lessons from a single center in the epicenter of the pandemic

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Abstract

The impact of coronavirus disease-19 (COVID-19) in liver recipients remains largely unknown. Most data derive from small retrospective series of patients transplanted years ago. We aimed to report a single-center case series of five consecutive patients in the early postoperative period of deceased-donor liver transplantation who developed nosocomial COVID-19. Two patients presented important respiratory discomfort and eventually died. One was 69 years old and had severe coronary disease. She rapidly worsened after COVID-19 diagnosis on 9th postoperative day. The other was 67 years old with non-alcoholic steatohepatitis, who experienced prolonged postoperative course, complicated with cytomegalovirus infection and kidney failure. He was diagnosed on 36th postoperative day and remained on mechanical ventilation for 20 days, ultimately succumbing of secondary bacterial infection. The third, fourth, and fifth patients were diagnosed on 10th, 11th, and 18th postoperative day, respectively, and presented satisfactory clinical evolution. These last two patients were severely immunosuppressed, since one underwent steroid bolus for acute cellular rejection and another also used anti-thymocyte globulin for treating steroid-resistant rejection. Our novel experience highlights that COVID-19 may negatively impact the postoperative course, especially in elder and obese patients with comorbidities, and draws attention to COVID-19 nosocomial spread in the early postoperative period.

KEYWORDS

COVID-19, liver transplantation, postoperative period, severe acute respiratory syndrome coronavirus 2

Abbreviations: ABTO, Brazilian Association of Organ Transplantation; ACR, acute cellular rejection; COVID-19, coronavirus disease-19; CT, computed tomography; DDLT, deceased-donor liver transplantation; HCC, hepatocellular carcinoma; ICU, intensive care unit; LT, liver transplantation; NASH, non-alcoholic steatohepatitis; NO, naso-oropharyngeal; OTI, orotracheal intubation; PMT, pulse methylprednisolone therapy; POD, postoperative day; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TACE, transarterial chemoembolization.

TABLE 1 Summary of cases with early postoperative COVID-19

Case	Age, sex, and BMI	Liver Disease	Comorbidities	Donor data	Surgical data	Immunosuppression protocol	COVID-19 symptoms	COVID-19 treatment and outcome
1	69 y, female BMI: 34.71 kg/m ²	HCV Downstaged HCC MELD: 15 Child-Pugh: A6	SAH Coronariopathy Pulmonary hypertension	Female, 45 y BD: hemorrhagic stroke	GW: 1600 g TST: 285 min TIT: 585 min WIT: 35 min BBP: None	Basiliximab, tacrolimus, mycophenolate and intraoperative corticoid bolus and tampering	9th POD Fever Mild dyspnea Diarrhea	OTI on 12th POD Azithromycin Death on 13th POD due to due to refractory shock and acidosis.
2	67 y, male BMI: 32.81 kg/m ²	NASH α1-antitripsin deficiency MELD: 13 Child-Pugh: B7 Hepatic encephalopathy	SHA Obesity	Female, 22 y BD: subarachnoid hemorrhage 21 d ICU AST 156 U/ml ALT 296 U/ml GGT 584 mg/dL	GW: 1475 g TST: 435 min TIT: 445 min WIT: 40 min BBP: None	Basiliximab, tacrolimus, mycophenolate and intraoperative corticoid bolus and tampering	36th POD Fever Hypoactive Delirium Progressive dyspnea	OTI on 37th POD Azithromycin Hydroxychloroquine Death on 56th POD due to secondary bacterial infection
3	69 y, male BMI: 27.58 kg/m ²	Alcoholic cirrhosis HCC MELD: 13 Child-Pugh: A6	SHA DM	Male, 54 y BD: cranioccephalic trauma	GW: 1370 g TST: 425 min TIT: 405 min WIT: 35 min BBP: None	Tacrolimus and intraoperative corticoids bolus with tampering	10th POD Fever watery diarrhea dry cough Mild exertional dyspnea	Venturi mask Supportive care Dyspnea worsened on 10th hospitalization day Discharged home on 17th hospitalization day
4	59 y, male BMI: 24.38 kg/m ²	Cryptogenic cirrhosis Ascites Hepatic encephalopathy MELD: 10 Child-Pugh: B7	Hepatosplenic schistosomiasis	Female, 52 y BD: hemorrhagic stroke Presented cardiac arrest before organ recovery	GW: 1450 g TST: 360 min TIT: 460 min WIT: 35 min BBP: None	Tacrolimus, mycophenolate and intraoperative corticoid bolus and tampering. Received PMT for acute cellular rejection treatment	11st POD Subfebrile temperature dry cough	Supportive care Discharged on 27th POD
5	34 y, male BMI: 22.38 kg/m ²	Sclerosing primary cholangitis MELD: 35 Child B7	None	Female, 42 y BD: ischemic stroke	GW: 1425 g TST: 395 min TIT: 360 min WIT: 35 min BBP: None	Tacrolimus and intraoperative corticoids bolus with tampering. Mycophenolate, PMT, anti-thymocyte globulin were later used due to steroid-resistant severe acute cellular rejection	18th POD: asymptomatic 24th POD: Fever Mild dyspnea	Supportive care Needle thoracocentesis drainage of pleural effusion Discharged home on 41st POD

Note: Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BBP, blood-borne products; BD, brain death; BMI, body mass index; DM, diabetes mellitus; GGT, gamma-glutamyl transferase; GW, graft weight; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; MELD, model of end-stage liver disease; NASH, non-alcoholic steatohepatitis; PMT, pulse methylprednisolone therapy POD, postoperative day; SHA, systemic artery hypertension; TIT, total ischemic time; TST, total surgery time; WIT, warm ischemic time.

1 | INTRODUCTION

Brazil is currently one of the most affected countries in the world by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and has become the epicenter of the coronavirus disease-19 (COVID-19) pandemic in Latin America.¹ The impact of COVID-19 in liver recipients remains largely unknown, as most data derive from case reports and small retrospective series.²⁻¹⁶ Moreover, most of them address patients who were transplanted years ago.^{2-6,8-10,12} Information regarding patients in the early postoperative period is very scarce.

Many authors recommend weaning of immunosuppression and some even advocate its complete withdrawal.^{2,4,9,12,16} Nevertheless, these suggestions are mostly based on patients in late postoperative period, for whom immunosuppression is already diminished and acute cellular rejection (ACR) is less likely. Another distinct feature is the impact of nosocomial infection, as these patients are generally infected in-hospital. When the pandemic starts its declining phase, community viral spread is expected to decrease; however, nosocomial infection may persist longer and affect more routinely hospitalized patients who just underwent transplantation.

São Paulo is Brazil's largest city and the current epicenter of the disease in the country. Our institution is one of largest transplantation centers in Latin America, having performed more than 3000 liver transplants (LT), with an average of 160 LT per year. The aim of this study was to report a single-center case series of consecutive patients in the early postoperative period of deceased-donor liver transplantation (DDLT) who developed COVID-19.

2 | CASE REPORTS

During the first months of the city quarantine (March 24th to May 31st, 2020), we performed 19 DDLT in 18 patients and diagnosed 5 cases of COVID-19 in the early postoperative period. In all cases, SARS-CoV-2 infection was confirmed via real-time polymerase chain reaction (RT-PCR) in naso-oro-pharyngeal (NO) swab or tracheal secretion. Nucleic acid (RNA) was extracted with an automated method based on magnetic beads (mSample Preparation System RNA, Abbott). Reverse transcription, amplification, and detection were performed following an in-house protocol validated in the Laboratory Division (College of American Pathologists accredited) comprising an E gene assay as the first-line screening tool, followed by confirmatory testing with a N gene assay, as previously described.¹⁷ Endogenous gene RNase P was used as internal control of extraction and amplification, as well as positive and negative external controls. Analytical sensitivity was 40 copies/mL, and specificity in samples containing other respiratory viruses RNA was 100%. Table 1 depicts a summary of all cases, and Table 2 shows laboratory assessment at time of COVID-19 diagnosis.

2.1 | Case 1

A 69 years old female patient was presented with hepatitis C virus infection DDLT due to cirrhosis and hepatocellular carcinoma (HCC), which were downstaged to within Milan criteria after 4 transarterial chemoembolization (TACE). Her past medical history was remarkable for systemic arterial hypertension, coronary disease, and pulmonary hypertension. Myocardial perfusion scintigraphy did not show any inactive areas and ejection fraction was 69% on echocardiogram, even though coronary angiography identified important stenosis (>80%) in the right posterior descending artery, descending anterior artery and circumflex artery.

The procedure went on uneventfully, and the patient was extubated on the 1st postoperative day (POD). Renal function was worsened, and dialysis was required from the 2nd POD. She presented with mild dyspnea, fever, and diarrhea on 9th POD. A thoracic computed tomography (CT) scan showed multiple bilateral ground-glass pulmonary opacities, occasionally associated with interlobular septa thickening and fine reticulate, affecting approximately 50% of the lung. A RT-PCR in NO swab confirmed SARS-CoV-2 infection, and she was started on azithromycin. The patient clinically worsened on 12th POD, presenting hypotension and massive dyspnea, and had to undergo orotracheal intubation (OTI). Despite immunosuppression discontinuation, she developed important hemodynamic instability and died on 13th POD due to refractory shock and acidosis.

2.2 | Case 2

A 67 years old male patient underwent DDLT 10 days before the COVID-19 quarantine was declared. He was a cirrhotic patient due to non-alcoholic steatohepatitis (NASH) and α 1-antitrypsin deficiency, who had additional points in waitlist because of hepatic encephalopathy. The postoperative course was remarkable for persistent need of hemodialysis. On 26th PO, liver enzymes were mildly elevated and he underwent a percutaneous liver biopsy, which did not show significant alterations, but cytomegalovirus infection was diagnosed (serum polymerase chain reaction: 213 458 IU/mL) and he was started on intravenous ganciclovir. On 36th POD, he was presented with fever, hypoactive delirium, and progressive dyspnea. Thoracic CT scan showed bilateral several ground-glass pulmonary opacities affecting approximately 50% of the lungs (Figure 1A,B). He underwent OTI due to persistent hypoxemia and respiratory discomfort. A RT-PCR in tracheal secretion was positive for SARS-CoV-2. He was then started on large-spectrum antibiotics (meropenem and vancomycin) for 14 days as well as oseltamivir, azithromycin, and hydroxychloroquine for 5 days. Mycophenolate was withdrawn, and tacrolimus serum level was maintained at around 5 mg/dL.

He remained on mechanical ventilation for 20 days. Ventilator-associated pneumonia was diagnosed on 53th POD with multiresistant *Acinetobacter baumannii* being identified on tracheal secretion, and he was started on colistin. His condition continued to deteriorate and he died of persistent hypoxemia and hemodynamic instability on 56th POD.

Laboratory test	Case 1	Case 2	Case 3	Case 4	Case 5
Alkaline phosphatase (U/L)	571	398	103	646	906
gamma-glutamyl transferase (U/L)	1288	1405	283	3211	2167
Total Bilirubin (mg/dL)	0.74	1.39	0.68	4.51	2.73
Direct Bilirubin (md/dL)	0.50	1.2	0.46	4.03	2.45
Aspartate aminotransferase (U/L)	251	121	53	116	43
Alanine aminotransferase (U/L)	150	137	106	209	65
Albumin (g/dL)	1.8	2.2	3.3	2.5	2.6
INR	–	1.1	1.07	1.06	1.10
Total leukocytes (/mm ³)	29 340	12 910	3130	24 850	14 740
Lymphocyte count (/mm ³) and percentage	1174 (4%)	387 (2.99%)	330 (10.54%)	1740 (7%)	737 (5%)
Creatinine (mg/dL) ^a	5.84	6.36	1.0	3.04	1.07
Urea (mg/dL) ^a	178	141	36	50	18
C-reactive protein (mg/L)	146.12	226.01	96.3	50.50	82.22
D-dimer (ug/mL)	8477	19 354	4626	2253	6489
Lactate dehydrogenase (U/L)	895	691	280	–	–
Ferritin (ng/mL)	–	2896	–	–	1558
Tacrolimus serum level (ng/mL)	10.8	13.1	13.3	13.4	13.7

^aPatients 1, 2, and 4 required renal replacement therapy.

2.3 | Case 3

A 69 years old male patient underwent DDLT due to alcoholic cirrhosis and HCC. Postoperative course was uneventful, and he was discharged home on 8th POD. He returned to the emergency department on 10th POD complaining of fever, watery diarrhea, dry cough, and mild exertional dyspnea. A thoracic CT scan showed bilateral multiple ground-glass pulmonary opacities (Figure 1C), affecting less than 50% of the lungs. He was started on oseltamivir for 5 days, piperacillin/ tazobactam for 7 days, and oral metronidazole for 10 days. An RT-PCR in NO swab was positive for SARS-CoV-2. Shortness of breath worsened on the 10th day of hospitalization. Another thoracic CT scan showed increase in number and dimensions of ground-glass opacities, now affecting more than 50% of the lungs (Figure 1D). He could nonetheless sustain adequate levels of O₂ saturation on Venture mask 50% and did not require further interventions, being discharged home on 17th hospitalization day.

2.4 | Case 4

A 59 years old male patient with cryptogenic cirrhosis underwent an uneventful DDLT. The patient was extubated on 1st POD, but required hemodialysis from the 4th POD. Pulse methylprednisolone therapy (PMT) was used on 6th POD due to ACR. On 11st POD, he

TABLE 2 Laboratory assessment on COVID-19 diagnosis

developed subfebrile temperature and dry cough, without need of oxygen therapy. A thoracic CT scan showed bilateral ground-glass pulmonary opacities, sometimes associated with thickening of interlobular septa and fine reticulate. An RT-PCR in NO swab confirmed SARS-CoV-2. Meropenem and Vancomycin were used for 3 days, and mycophenolate was withdrawn. The patient presented satisfactory evolution and did not require further interventions, being discharged on 27th POD.

2.5 | Case 5

A 34 years old male patient with sclerosing primary cholangitis and cirrhosis underwent DDLT with biliodigestive anastomosis. Postoperative evolution was complicated by severe ACR, which did not respond to PMT. He underwent percutaneous liver biopsy, which complicated with hemorrhage and required exploratory laparotomy to evacuate blood clots on 11st POD. Owing to the diagnosis of steroid-resistant severe ACR, mycophenolate and anti-thymocyte globulin were introduced. On 18th POD, an abdominal CT scan performed to evaluate the presence of retained clots showed some ground-glass opacities in the base of the left lung. He started with fever and mild dyspnea on 24th POD and RT-PCR in NO swab confirmed SARS-CoV-2. A thoracic CT scan showed numerous bilateral peribronchovascular ground-glass opacities, mainly in the upper

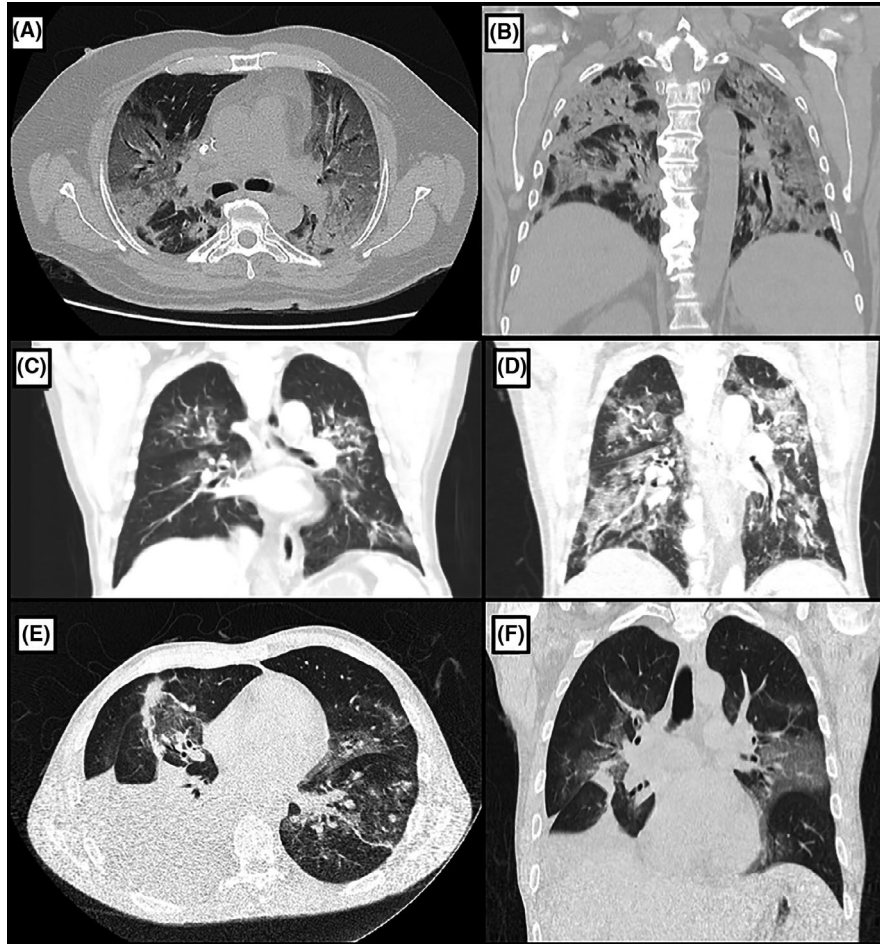


FIGURE 1 A and B, Thoracic computed tomography (CT) scan of patient 2, showing bilateral several ground-glass pulmonary opacities affecting approximately 50% of the lungs, occasionally associated with thickening of interlobular septa and thin reticulate, in addition to peripheral sparse consolidation foci with greater extension in the posterior aspect of the lower lobes (A—axial view, B—coronal view). C, Thoracic CT scan of patient 3 on 10th postoperative day (POD), showing bilateral multiple ground-glass pulmonary opacities, sometimes associated with thickening of interlobular septa and fine reticulate, affecting less than 50% of the lungs. D, Thoracic CT scan of the same patient on 20th POD, performed due to shortness of breath worsening, revealing increase in number and dimensions of ground-glass pulmonary opacities, now affecting more than 50% of the lungs. E and F, Thoracic CT scan of patient 5, showing numerous bilateral peribronchovascular ground-glass opacities, mainly in the upper lobes, some with thickening of the inter and intralobular septa. There is also a large pleural effusion on the right side with restrictive atelectasis of the adjacent pulmonary parenchyma (E—axial view, F—coronal view)

lobes. Almost total atelectasis of the right lower lobe due to adjacent pleural effusion was also noted, which was eventually drained via needle thoracocentesis (Figure 1E,F). Despite the more aggressive immunosuppression, the patient remained well with adequate O_2 saturation on oxygen catheter and was discharged home on 41st POD.

3 | DISCUSSION

This report represents one of the largest series of liver transplant recipients in early postoperative with nosocomial COVID-19. Fever and respiratory symptoms were present in all cases, and gastrointestinal manifestations were observed in two. We could identify two patterns of clinical evolution: some patients presented mild disease while others required mechanical ventilation and eventually died.

As appointed for post-transplant patients with long-term metabolic complications,³ comorbidities seem to outweigh immunosuppression in determining prognosis even in the early postoperative period. In fact, one patient with unfavorable outcome had severe coronary disease and the other one experienced prolonged postoperative course complicated with CMV infection and kidney failure. Both were also obese. Whereas the first patient developed SARS-CoV-2 infection and rapidly progressed to death, the second exhibited a more insidious course and ultimately died of secondary bacterial infection. Regarding laboratory assessment, a wide variation in liver enzymes was observed, probably related to the particular evolution of each case before COVID-19 diagnosis. However, inflammatory markers and D-dimer were elevated in all cases, even though they are not specific for COVID-19.

Regarding the specify treatment of COVID-19, we followed our institution's protocol, in which most novel drugs, such as umifenovir,

lopinavir/ritonavir, and tocilizumab,^{2,4,9,12,16} are used under clinical trials. Patients 1 and 2 developed severe COVID-19 and required OTI. They were started on azithromycin, but hydroxychloroquine was used only in the second case, because the first one rapidly progressed to death. Hydroxychloroquine was initially recommended, but is no longer used given the latest evidence. Large-spectrum antibiotics were used in patients 3 and 4 aiming to cover bacterial infection as well; however, as they presented satisfactory clinical evolution, no additional treatment was performed. Patient 5 experienced mild symptoms and successfully responded to supportive care.

Immunosuppression was completely withdrawn in case 1, due to the patient's dramatic worsening. In case 2, mycophenolate was discontinued and tacrolimus serum levels were lowered. In case 4, mycophenolate was also discontinued, but no changes were made in tacrolimus serum levels. In cases 3 and 5, immunosuppression was not altered. The risk of ACR is higher in early transplanted patients and, in fact, it occurred in 2 early cases previously described in literature.^{7,13} It seems that immunosuppression must be tailored on a case-by-case basis according to the clinical evolution. For instance, patient 4 underwent PMT before COVID-19 diagnosis due to ACR and patient 5 underwent PMT and anti-thymocyte globulin infusion owing to steroid-resistant ACR. Despite being severely immunosuppressed, they presented only mild symptoms.

As a public quaternary center, our institution was prepared to be the main reference center of COVID-19 cases in São Paulo State at the beginning of April, 2020. As the number of transplants in the context of COVID-19 pandemic has decreased substantially,^{16,18,19} strategies have been developed for ensuring the availability of transplantation activity, such as establishment of hospital areas especially dedicated to non-COVID-19 patients.^{20,21} The main building of our institution was then designated exclusively for treating patients with COVID-19 when the quarantine was declared, while the nearby institutes were considered areas with low exposure to SARS-CoV-2. Organ transplantation activities were supposed to continue in wards and ICUs without SARS-CoV-2-infected patients. Furthermore, all deceased donors were screened to SARS-CoV-2 via RT-PCR in NO swab and all recipients performed a thoracic CT scan before hospital admission, in accordance with Brazilian Association of Organ Transplantation (ABTO) recommendations, except patient 2 who was transplanted immediately before the implementation of these measures. All donors tested negative for SARS-CoV-2, and no alterations were noted on recipients CT scans.

The incubation period for SARS-CoV-2 is usually 5-6 days; however, it may reach 14 days.²¹ Therefore, it is possible that 3 patients (cases 1, 3, and 4) might have been admitted to the hospital already infected. We consider this hypothesis unlikely, since all of them were clinically asymptomatic and with no radiological sign, and there was an ongoing nosocomial outbreak of COVID-19 in our institution at that time, with many non-transplant patients from others non-COVID-19 wards developing the disease. Therefore, it is reasonably safe to assume that we experienced a

nosocomial spread of the virus, probably carried out by asymptomatic patients, or even by patient's visitors and healthcare personnel. Due to these events, infection control protocols were tightened, including a temporary ban on family visits, strengthening of barriers precautions, and mass SARS-CoV-2 screening for healthcare professionals. We also included the RT-PCR for SARS-CoV-2 in NO swab in the recipients screening. Although those infection control protocols with strict barrier precautions may reduce SARS-CoV-2 nosocomial spread even in immunosuppressed patients,²² the challenge of maintaining large liver transplant programs in areas with high community transmission of SARS-CoV-2 will remain until a vaccine is developed.

In conclusion, we reported a case series of liver recipients who developed SARS-CoV-2 infection in the early postoperative period, probably related to a nosocomial outbreak. Our experience highlights that COVID-19 may impact negatively the postoperative course, especially in elder and obese patients with comorbidities, and draws attention to COVID-19 nosocomial spread.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest with regards to the content of this manuscript.

AUTHOR CONTRIBUTIONS

DRW, EA, and LSN involved in conceptualization and wrote the original draft. VR, LNG, RBM, RSP, and RMA investigated the study. CSL and LMM involved in resources. LBH, LD, and DRT involved in data curation. FHG and WA wrote, reviewed, and edited the study. LAC involved in supervision.

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