Severe COVID-19 after liver transplantation, surviving the pitfalls of learning on-the-go: Three case reports

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Abstract

BACKGROUND
The novel coronavirus 2019 (COVID-19) pandemic has dramatically transformed the care of the liver transplant patient. In patients who are immunosuppressed and with multiple comorbidities, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with increased severity and mortality. The main objective of this report is to communicate our experience in the therapeutic management of SARS-CoV-2 infection in 3 liver transplant patients. Secondly, we stress the management and investigation of the contagious spreading into a liver transplant ward.

CASE SUMMARY
Campos PA, Pons JA, Martinez M, Valiente-Campos J, Gajownik U, Ortiz ML, Parrilla P, Robles R, Sánchez-Bueno F, Moreno S and Ramírez approved of the final version to be published.

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INTRODUCTION

After the first cases of coronavirus-2 pneumonia (SARS-CoV-2) were detected in early December 2019 in Wuhan (Hubei, China)[2,3], a pandemic has overtaken hundreds of countries[4]. The main active sources are currently located in Europe and the United States[5]. This medical emergency has tested global healthcare systems, which have established strategic changes and protocols to prioritize healthcare and avoid overloading. The frequency of liver transplantation operations has been seriously affected. Transplant programs depend on the availability of donors, the vast majority of whom are deceased, and medical personnel normally oversee these programs in intensive care units, but these facilities are currently overcrowded. The result of these conditions has been a dramatic decrease in activity in all transplant groups around the world. In Spain, the world leader in organ donation, surgeons had access to the livers of about 100 deceased donors per week during the 3-month period before the detection of the first case of novel coronavirus (COVID-19); this number has since dropped dramatically to a level of only 15 donors per week[6,7].

In an effort to contain the pandemic, drastic community measures of social confinement and distancing have been established, and these measures extend to the healthcare environment, enhancing telematic activities for the ambulatory management of patients. At the in-hospital level, most of the preventive measures are aimed at preventing the spread of infection by healthcare professionals during the care of COVID-19 patients. The impact of nosocomial infection by COVID-19 has warranted little attention and could be especially relevant to transplant recipients during their hospitalization.

The main objective of our work is to communicate our experience in the therapeutic management of severe SARS-CoV-2 infection in three liver transplant patients who required invasive mechanical ventilation, two of whom had an infection of nosocomial

CONCLUSION

We illustrate in detail the evolution of a nosocomial COVID-19 outbreak in a liver transplant ward. We believe that these findings will contribute to a better understanding of the natural history of the disease and will improve the treatment of the liver transplant patient with COVID-19.

Key Words: Liver transplantation; COVID-19; SARS-CoV-2; Cross infection; Nosocomial infection; Case report

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Core Tip: In patients who are immunosuppressed and with multiple comorbidities, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with increased severity and mortality. We report our experience in the therapeutic management of SARS-CoV-2 infection in 3 liver transplant patients and stress the management and investigation of a contagious spreading into a liver transplant ward.

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CASE PRESENTATION

Since the detection of the first case of COVID-19 in our region on March 8, 2020, and until May 31st, 2020, a total of twelve liver transplant patients have been hospitalized in our liver transplant unit.

Chief complaints

Case 1: Sixty-one-year-old woman with a liver transplant in September 2019 for cryptogenic cirrhosis. In early March, she was admitted for diarrhea, and a few days later she developed acute respiratory failure, and heart failure. A first RT-PCR of SARS-CoV-2 from throat and pharyngeal swabs was negative but became positive three days later after a second RT-PCR was conducted due to high clinical suspicion (Figure 1). Treatment with hydroxychloroquine and lopinavir/ritonavir was then initiated, adjusting the tacrolimus levels, but the patient suffered progressive clinical and analytical worsening, with the need for invasive mechanical ventilation, associated with pulmonary superinfection by *Enterococcus faecalis* and *Enterococcus faecium* detected in bronchoalveolar lavage fluid. Finally, the patient developed shock with multisystem failure and died in the third week of hospitalization.

Case 2: Sixty-eight-year-old male, transplanted on March 4, 2020, by non-alcoholic steatohepatitis. During the immediate post-transplant period, he was diagnosed with a biliary stricture and was treated endoscopically. His wife, the primary caregiver, tested positive for SARS-CoV-2 via RT-PCR from pharyngeal swabs on March 18, 2020, after reporting slightly compatible symptoms. All staff in contact with her, including the patient himself (who was initially negative), were evaluated with RT-PCR. Of a total of 40 people tested, one hepatologist was positive for SARS-CoV-2; this physician was in contact with all patients admitted at that time. Four days later, the patient, without symptoms, was discharged. Two days after discharge, the patient was readmitted for fever and cough, and the RT-PCR of SARS-CoV-2 was positive (Figure 1). Early treatment with hydroxychloroquine and azithromycin was initiated, adjusting the doses of mycophenolic acid and tacrolimus. Seven days after the positive result, the patient was admitted to the intensive care unit due to deterioration of respiratory function requiring invasive mechanical ventilation and treatment with tocilizumab. The patient progressed satisfactorily to home discharge and asymptomatic, but still with a positive RT-PCR of SARS-CoV-2 two months later.

Case 3: Sixty-two-year-old woman who received a liver transplant in February 2019 secondary to primary biliary cholangitis and was discharged in the first week of March 2020 after an episode of constitutional syndrome. On April 6, 2020, she was readmitted with fever, dyspnea, and diarrhea, with a RT-PCR positive for SARS-CoV-2. Forty-eight hours later, the patient progressively deteriorated, requiring admission to intensive care unit with invasive mechanical ventilation, and was treated with tocilizumab in addition to hydroxychloroquine, azithromycin, and methylprednisolone. Mycophenolic acid was suspended, and doses of tacrolimus were reduced to the minimum necessary. After four days of invasive mechanical ventilation, extubation was performed. In spite of the measures adopted, the patient evolved severely. Two months after the onset of the outbreak, and still with a positive RT-PCR of SARS-CoV-2, she developed a tracheoesophageal fistula. An esophageal prosthesis and an extracorporeal venovenous membrane oxygenation (vv-ECMO) were placed. Forty-five days after the first positive RT-PCR of SARS-CoV-2 the virus was negative in the RT-PCR of the bronchoalveolar lavage. Unfortunately, the patient died eighty days after the onset of the outbreak in our liver transplant unit.

History of present illness

A cluster of three patients who temporarily coincided in the hospitalization ward developed a SARS-CoV-2 [reverse transcription polymerase chain reaction (RT-PCR) throat swab] infection. Given the use of anonymous clinical data and the observational approach of our paper, our work was exempt from approval from an ethics' board. **Table 1** shows the main clinical features of these three patients. It is important to note that the wife of case 2, one hepatologist on the transplant team, and three nurses in the ward were also infected with the SARS-CoV-2 virus.

In our transplant unit, the outbreak of SARS-CoV-2 began on March 18. After a
Table 1 Details of the three cases reported

| Case 1                          | Case 2                          | Case 3                          |
|---------------------------------|---------------------------------|---------------------------------|
| **Age (yr)**                    | 61                              | 68                              | 62                              |
| **Sex**                         | Female                          | Male                            | Female                          |
| **LT indication**               | Cryptogenic cirrhosis           | NASH                            | Primary biliary cholangitis     |
| **Date of liver transplant**    | September 7, 2019               | March 3, 2020                   | February 13, 2019               |
| **Immunosuppression (per day)** | Tacrolimus 5 mg and prednisone 5 mg | Tacrolimus 7 mg, mycophenolic acid 2000 mg, prednisone 20 mg | Tacrolimus 3 mg, mycophenolic acid 2000 mg, prednisone 5 mg |
| **Blood concentration of tacrolimus (before COVID-19)** | 7 ng/mL                          | 7.5 ng/mL                       | 5.2 ng/mL                       |
| **Comorbidities**               | Hypothyroidism                  | Diabetes, hypertension, stroke  | Hypertension                    |
| **Laboratory test:**            |                                 |                                 |                                 |
| PaO₂/FiO₂ ratio (while IMV)      | 237 (76-376)                    | 367 (337-385)                   | 256 (133-329)                   |
| White-cell count (× 10⁹/UL)     | 4.50 (2.38-9.87)                | 6.61 (1.8-17.4)                 | 15.71 (7.02-36.14)              |
| Lymphocyte count (× 10⁹/UL)     | 0.30 (0-0.65)                   | 0.325 (0.2-1.02)                | 1 (0.54-2.01)                   |
| Platelet count (× 10⁹/UL)       | 9.5 (3-38)                      | 113.5 (37-372)                  | 290 (158-406)                   |
| Hemoglobin (g/DL)               | 8.7 (6.5-9.4)                   | 9.2 (7-11.8)                    | 10.4 (7.6-12.9)                 |
| IL-6 (pg/mL)                    | 599 (400-799)                   | 558 (192-1000)                  | 54 (50-286)                     |
| C-reactive protein (mg/DL)      | 10.3 (8.2-18.3)                 | 4 (0.4-13.3)                    | 1.8 (0.7-4.6)                   |
| Ferritin (mg/mL)                | 2.2 (1.1-7.8)                   | 0.25 (0.12-0.43)                | 0.28 (0.17-0.75)                |
| Lactate dehydrogenase (U/L)     | 5338 (814-9862)                 | 1262 (392-2095)                 | 2047 (1360-2297)                |
| Aspartate aminotransferase (U/L) | 126 (29-466)                    | 14 (9-36)                       | 30 (16-44)                      |
| Alanine aminotransferase (U/L)  | 89 (29-197)                     | 21 (8-31)                       | 24 (5-98)                       |
| Total bilirubin (mg/DL)         | 1.2 (0.3-2.65)                  | 0.56 (0.39-1.25)                | 1.82 (0.21-4)                   |
| Creatine kinase (U/L)           | 14 (10-18)                      | 13 (7-75)                       | 29 (29-36)                      |
| Creatinine (mg/DL)              | 0.69 (0.45-1.07)                | 1.22 (1.04-1.93)                | 0.89 (0.54-2.65)                |
| D-dimer (mg/mL)                 | 1071 (565-1825)                 | 1347 (620 - 3431)               | 283 (153-648)                   |
| Sodium (meq/L)                  | 137 (128-141)                   | 139 (136 - 163)                 | 141 (135-145)                   |
| Potassium (meq/L)               | 4.6 (2.9-5.8)                   | 4 (3.3-4.9)                     | 4 (3.2-5.2)                     |
| Chloride (meq/L)                | 102 (97-105)                    | 103 (100-111)                   | 107 (99-112)                    |
| RT-PCR of SARS-CoV-2            | Negative on day 3; positive on day 6 | Negative on day 8; positive on days 13, 36, 42, 47, 54, 65 and 79 | Negative on days 14, 72 and 75; positive on days 26, 42 and 55 |
| Radiologic findings             | Bilateral pneumonia, pleural effusion | Bilateral pneumonia, peripheral ground-glass opacity, pleural effusion | Bilateral pneumonia, peripheral ground-glass opacity |
| Treatment                       | HCQ (200 mg daily), azithromycin (250 mg daily), LPV/r (one dose 400/100 mg), vancomycin (1 g daily) | HCQ (200 mg daily), azithromycin (250 mg daily), tocilizumab (one dose 8 mg/kg), methylprednisolone (180 mg three doses) | HCQ (200 mg daily), azithromycin (250 mg daily), tocilizumab (one dose 8 mg/kg), methylprednisolone (60 mg daily), vv-ECMO |
| Immunosuppressant dose reduction | Yes (low dose of tacrolimus)     | Yes (mycophenolic acid suspended and low dose of tacrolimus) | Yes (mycophenolic acid suspended) |
| Rejection during or after COVID-19 | No                              | No                              | Yes                             |
| Complications                   | Secondary *Enterococcus faecalis* | Asymptomatic intra-abdominal    | Tracheoesophageal fistula        |

*Data presented as median (IQR).*
positive RT-PCR result in case 1, the wife of case 2 also tested positive after reporting a fever and neck pain. Without delay, we conducted an exhaustive investigation on all the members of the unit (25 nurses and assistants, two cleaning staff, one warden, and nine physicians), with one nursing assistant testing positive for SARS-CoV-2 (hospital admission for ten days for pneumonia, without the need for intensive care unit), two nurses testing positive (one with a mild symptoms and negative RT-PCR at one month, and the other asymptomatic and negative at 13 d), and a hepatologist testing positive (negative at 15 d, asymptomatic and no admission).

**Physical examination**

The remaining healthcare personnel who tested negative for SARS-CoV-2 were placed in preventive home confinement for 14 d, with negative RT-PCR determinations of SARS-CoV-2 thereafter. In addition, the hospital ward was closed for complete disinfection.

**Further diagnostic work-up**

Figure 2 shows the epidemiological timeline of the three positive liver transplant recipients as well as the four contacts in the ward (one doctor, one assistant, and two nurses) who tested positive for SARS-CoV-2.

**FINAL DIAGNOSIS**

The final diagnosis of the presented cases is severe COVID-19 after liver transplantation.

**TREATMENT**

Case 1 was treated with Hydroxychloroquine (HCQ, 200 mg daily), azithromycin (250 mg daily), lopinavir/ritonavir (one dose 400/100 mg) and vancomycin (1 g daily). The patient in case 2, underwent a treatment that included HCQ (200 mg daily), azithromycin (250 mg daily), tocilizumab (one dose 8 mg/kg) and methylprednisolone (180 mg three doses). In the case of patient 3, however, the outcome was more severe and required the use of a vv-ECMO in addition to HCQ (200 mg daily), azithromycin (250 mg daily), tocilizumab (one dose 8 mg/kg) and methylprednisolone (60 mg daily) (Table 1 and Figure 1).

**OUTCOME AND FOLLOW-UP**

All three patients required intensive care unit admission and invasive mechanical ventilation (Figure 1). Two of them (cases 1 and 3) progressed severely until death. The other one (case 2), who received tocilizumab, had a good recovery. In the outbreak, the wife of one of the patients and four healthcare professionals involved in their care were also infected (Figure 2).

**DISCUSSION**

The most appropriate management for transplant recipients who develop COVID-19 and the impact of the infection on this population are not well known. In a previous publication on a population of 111 liver transplant patients with more than ten years of evolution and residents in lombardy (the epicentre of the pandemic in Italy), three
Figure 1  Clinical evolution of each case in a chronological perspective. A: (Case 1) Although the first reverse transcription polymerase chain reaction of severe acute respiratory syndrome coronavirus 2 was negative for the first few days, dyspnea became worse requiring intensive care unit admission. A single dose of lopinavir/ritonavir was administered on day 7; B: (Case 2) A dose of tocilizumab was administered on day 33. The patient improved progressively until he was discharged home; and C: (Case 3) A dose of tocilizumab was administered on day 28. The patient suffered a progressive worsening. A tracheoesophageal fistula was detected and an oesophageal prosthesis was placed. In addition, a venovenous extracorporeal membrane oxygenation was implemented to improve the patient’s oxygenation. BAL: Bronchoalveolar lavage; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; LPV/r: Lopinavir/ritonavir; NIV: Non-invasive ventilation; RT-PCR: Reverse transcription polymerase chain reaction; vv-ECMO: Venovenous extracorporeal membrane oxygenation.
The vast majority of measures to prevent infection in the population are focused on non-hospital settings (such as confinement and telemedicine). In hospitals, these measures are preferably designed to prevent the transmission of COVID-19 from patients to healthcare personnel, where the use of personal protective equipment is mandatory. Furthermore, in the case of patients with liver disease, additional measures must be taken. Xiao et al.[8] suggest, for example, that the communication between patients and medical staff should be done online and each patient taken care of by one attending doctor and one nurse exclusively.

Preventive measures should begin as soon as the recipient is admitted, including the
existence of a specific safety circuit until the result of the RT-PCR is known. For example, two of our patients who were candidates for transplant in the last week have tested positive on the day of the transplant but had no symptoms, and the donor grafts were therefore transplanted to other recipients. In addition to community transmission (case 1), nosocomial transmission of the virus must also be considered (cases 2 and 3). Once a case of nosocomial transmission is discovered, special measures should be applied not only to ward staff but also to all ward patients and facilities. In our experience after case 2, the entire ward was evacuated, and a procedure of disinfection and a quarantine of the premises and of all healthcare staff who had worked on the ward were undertaken.

Another problem in relation to the in-hospital management of SARS-CoV-2–infected transplant patients resides in the discordance between the positivity of RT-PCR and the symptoms suggestive of COVID-19, indicating a high-risk window of infection\cite{27}. As other published works have examined\cite{28,29}, in the outbreak that took place in our unit, there was a period in which healthcare professionals and companions who were asymptomatic carriers of SARS-CoV-2 concurred in space and time with other patients and healthcare professionals who did not have the virus. These circumstances favored the propagation of the virus until the first positive case was detected and the necessary measures were taken.

A final, equally important aspect is the real impact of the COVID-19 pandemic on organ donation, transplant policies, and waiting list mortality, which altogether constitute the so-called “indirect mortality” from SARS-CoV-2. Most countries have implemented emergency policies to prevent contagion, ranging from issuing systematic screening tests for SARS-CoV-2 in all donors and recipients, limiting donation to far from the hospital where the graft will be implanted, restricting liver transplant activity only in acute liver failure or critical patients\cite{29,30}, and implementing telemedicine in outpatient follow-up. In these circumstances, increases in both mortality among those on the waiting list and in the number of drop-outs due to clinical worsening or tumour progression (indirect deaths from COVID-19) are to be expected. In fact, in Spain, organ donation and transplantation have decreased dramatically. Before the declaration of the state of alarm on March 13, 2020, there were 7.2 donors and 16 transplants per day on average, but since that date, the rates have fallen to an average of 1.2 donors and 2.1 transplants per day\cite{31}.

**CONCLUSION**

Therefore, there are several lessons learned from our experience. Firstly, early administration of anti-IL-6 monoclonal antibodies could be beneficial in slowing down the cytokine storm in critically ill patients with COVID-19. Secondly, the disease
prodrome in two patients were the gastrointestinal and not the respiratory symptoms. Finally, COVID-19 is highly contagious, so drastic preventive measures and exhaustive epidemiological investigations must be conducted in the case of clinical suspected disease in the ward, even if the RT-PCR of SARS-CoV-2 has been tested negative.

Many uncertainties persist in relation to the diagnosis, treatment, and management of COVID-19 in liver transplant patients. It is certain that we will learn more about the disease and able to treat it more effectively in the coming months. In the meantime, we are walking blind, and we must rely on our scarce previous experience, on our intuition, and on the oldest methodology in medicine: Trial and error.

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