



# A Case Series of Variable Manifestations of COVID-19 in Liver Transplant Recipients

Behzad Hatami<sup>1</sup>, Amirhassan Rabbani<sup>2</sup>, Pardis Ketabi Moghadam<sup>1,\*</sup>, Mohsen Rajabnia<sup>1</sup>, Hamed Borhany<sup>3</sup>

1. Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Assistant Professor of Surgery, Taleghani Hospital, Department of Transplant & Hepatobiliary Surgery, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Resident of Internal Medicine, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

**\* Corresponding Author:**

Pardis Ketabi Moghadam, MD  
Address : Taleghani hospital, Yaman street, Chamran highway, Tehran, Iran

Tel : + 98 21 22432560  
Fax : + 98 21 22432570  
Email : ketabimoghadam.p@gmail.com

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## ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) that is known as COVID-19 is a new emerging respiratory infection attributed to novel coronavirus, firstly introduced in Wuhan, China, at the end of 2019. This infection is still of great concern because of various presentations of the disease, which are not fully understood. The manifestations of this virus among liver transplanted patients would be more challenging in the setting of immunosuppression. The focus of this study is to introduce different presentations of this virus in five liver transplant recipients referred to the gastroenterology ward of Taleghani Hospital, a teaching referral hospital in Tehran, Iran. These patients were started on different types of therapies for coronavirus infection, from only supportive care up to remdesivir infusion and hemoperfusion based on the severity of the disease. Additionally, they were advised to continue all their immunosuppressant agents with adjustment except for CellCept that was withheld.

## KEYWORDS:

COVID-19; Liver Transplant; Recipients; Iran

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## INTRODUCTION

It is not illogical to say that the novel coronavirus is a multifaceted virus with several presentations, including mild respiratory symptoms, acute respiratory distress syndrome (ARDS), mild to severe gastrointestinal (GI) symptoms, neurological involvement, altered smell, and taste sensations, headache, and thromboembolic events.<sup>1,2,3</sup> We owe our knowledge about the virus, its clinical manifestation, and its management to the case reports and case series around the world. But these studies are far fewer than we could be able to corroborate. So, more studies are required to identify all presentations of the novel virus particularly in immunosuppressed groups of patients like liver transplant recipients.

## CASE REPORTS

**Case-1:** A 61-year-old woman, known case of a recent liver transplantation since 2 months ago due to non-alcoholic steatohepatitis cirrhosis with a history of diabetes mellitus, chronic kidney disease, and hypertension

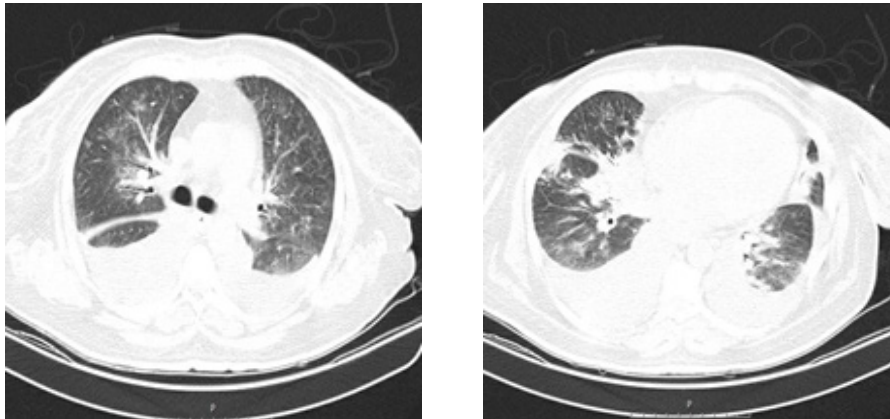


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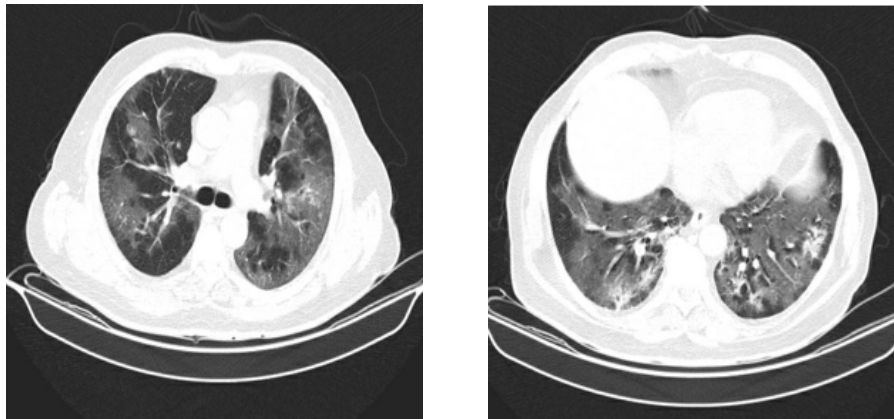
presented to the liver clinic of Taleghani Hospital, a liver transplantation center, Tehran, Iran with complaints of fever and generalized malaise. She was on insulin, prednisolone 7.5 mg per day, amlodipine, aspirin, everolimus 2 mg twice daily, and myfortic 720 mg twice daily. She denied any change in bowel habits and eating patterns except for slight nausea and decreased appetite. On admission, she was pale, and her vital signs were stable except for an O<sub>2</sub> saturation of about 85-90% on room air. Her physical exam was only notable for dullness to percussion and mild crackles in the lower lobes. There was mild tenderness at the incision site without signs of erythema or inflammation. A complete blood count revealed pancytopenia with a severe lymphopenia as presented with white blood cells (WBC): 1600 cells per cubic millimeter (reference range: 3400-9600 cells/mcL) with 15% lymphocytes and 85% polymorphonuclears, hemoglobin (Hb): 7.7 gr/dL (reference range in women: 12.1-15.1 gr/dL) and platelet (plt) count: 96000 per microliter (reference range: 150000-450000 per microliter). Further evaluation of anemia demonstrated normocytic and normochromic anemia with a serum iron profile compatible with anemia of chronic disease presented with decreased levels of serum iron and transferrin iron-binding capacity (TIBC), but with an elevation in the level of ferritin as an acute phase reactant. Serum creatinine level showed an increase of about 1.6-1.7 mg/dL (reference range: 0.84-1.21 mg/dL), which was constant in comparison with the previous creatinine tests suggesting a chronic kidney disease. Liver function tests, coagulation tests, and serum bilirubin levels were all within normal limits, which argued against the diagnosis of acute rejection. Abdominopelvic ultrasonography showed a normal liver transplant parenchyma and normal postoperative Doppler evaluation of hepatic vasculature. Secondary tests for *cytomegalovirus (CMV)* real-time-polymerase chain reaction (rt-PCR) and other opportunistic infections were all negative. A chest spiral computed tomography (CT) revealed bilateral multifocal ground-glass opacities in the lower lobes compatible with a viral infection, including COVID-19. Cardiomegaly, septal thickening, bilateral pleural effusion, and mosaic attenuation indicative of congestive heart failure (CHF) were also detected (figure-1). Cardiologists

were consulted, and treatment for CHF was started. A positive rt-PCR for COVID-19 infection confirmed the diagnosis. On admission, myfortic was discontinued, and the dose of prednisolone and everolimus was adjusted. She was started on intravenous (IV) fluids and oxygen (O<sub>2</sub>) saturation monitoring. In addition, slow remdesivir IV infusion (200 mg for the first day and 100 mg daily thereafter) was started. 7 days post-admission with receiving hydroxychloroquine and remdesivir, she was found to be clinically well, and she was discharged to continue the quarantine period at home.

**Case-2** : A 56-year-old man was admitted to the Emergency Department of Taleghani Hospital with fever, myalgia, and severe dyspnea. His medical history was remarkable for liver transplantation last year with the background of having cryptogenic cirrhosis. On admission, he was critically ill and obtunded. He had altered vital signs with a blood pressure of 160/85 mmHg, tachypnea with a respiratory rate of 22 times per minute, and tachycardia with a heart rate of 120 beats per minute. During admission, he spiked a temperature of 38.5<sup>o</sup>C. He has been on immunosuppressant agents, including prednisolone 10 mg daily, CellCept 1500 mg twice-daily, and tacrolimus 3 mg twice daily for 1 year. His laboratory tests revealed severe lymphopenia (WBC:1200 cells per cubic millimeter with 12% lymphocytes) and normochromic normocytic anemia of about 11.5 gr/dL (reference range for men:13.8-17.2 gr/dL). His liver enzymes were near the upper limit of normal with aspartate aminotransferase of 37 IU/L (reference range: 5-40 IU/L), alanine aminotransferase: 41 IU/L (reference range:7-46 IU/L), and alkaline phosphatase: 224 IU/mL (reference range: 80-320) and total serum bilirubin of about 1.9 mg/dL (reference range: 0.1-1.9). Arterial blood gas analysis demonstrated acute respiratory acidosis. O<sub>2</sub> saturation was 72% in room air; therefore, he went on ventilation by reservoir bag. His physical exam, except for disseminated crackles all over the lungs, more prominently in the basal areas of the lungs, was otherwise nremarkable. His spiral chest CT was reported to have disseminated bilateral multifocal ground-glass opacities consistent with COVID-19 infection (figure 2). Secondary evaluations



**Fig.1(A, B):** Bilateral multifocal ground-glass opacities in the lower lobes compatible with COVID-19 in addition to cardiomegaly, septal thickening, bilateral pleural effusion, and mosaic attenuation indicative of congestive heart failure are seen



**Fig. 2 (A,B):** Disseminated bilateral multifocal ground glass opacities with peripheral distribution consistent with COVID-19 infection

for opportunistic infections in an immunosuppressed patient were all negative. Rt-PCR for COVID-19 was positive. He started to receive slow remdesivir IV infusion (200 mg for the first day and 100 mg daily thereafter) and broad-spectrum antibiotics. Cellcept was stopped, prednisolone and tacrolimus were continued. During his admission, he continued to deteriorate, and finally, he underwent mechanical ventilation because of ARDS. Besides standard treatments, he underwent hemoperfusion (HA230 cartridge) as supportive therapy for COVID-19, but he was unresponsive to treatments and was expired.

**Case-3:** A 30-year-old woman who had a history of liver transplantation due to autoimmune hepatitis since 5 years earlier was referred to the Gastroenterology Clinic of Taleghani Hospital with gastrointestinal symptoms like fever, chills, watery diarrhea, nausea, vomiting, abdominal pain, and anorexia. Just after admission, physical examination except for mild

tachypnea and tachycardia attributed to a body temperature of about 39°C was otherwise unremarkable. Her blood pressure was 120/75 mmHg. Her chest spiral CT scan showed no specific abnormality (Figure 3). Her liver function profile showed aspartate aminotransferase (AST): 18 IU/L, alanine aminotransferase (ALT): 15 IU/L, alkaline phosphatase (ALP): 254 IU/L, total bilirubin: 0.4 mg/dL, direct bilirubin: 0.2 mg/dL, albumin: 3.8 gr/dL, WBC: 10100 cells per cubic millimeter, Hb: 10.1 gr/dL, Plt: 310000 per microliter, PT=13 seconds, INR=1, and PTT=32 seconds. The stool exam was unremarkable. Urine, blood, and stool cultures were all negative. Inflammatory markers were as follows: C-reactive protein (CRP): 18 mg/L and erythrocyte sedimentation rate (ESR): 22 mm/hr. Kidney function tests and serum electrolytes were all within normal limits. Level of tacrolimus was 8.7 ng/mL, which was an acceptable level for a liver transplant recipient. CMV rt-PCR and stool toxin

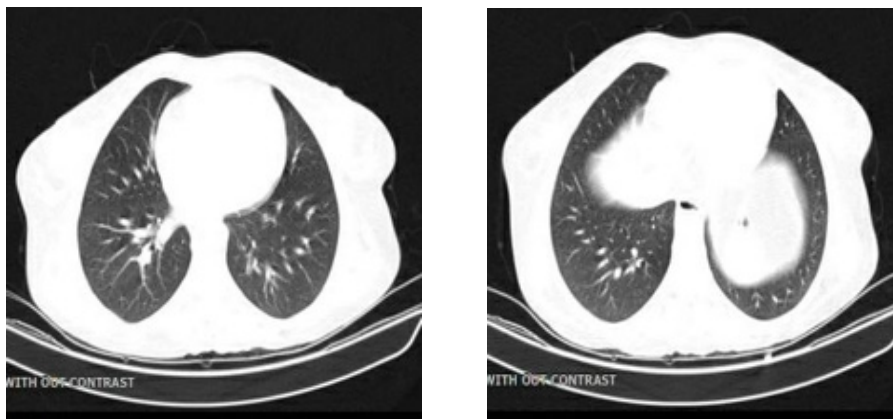


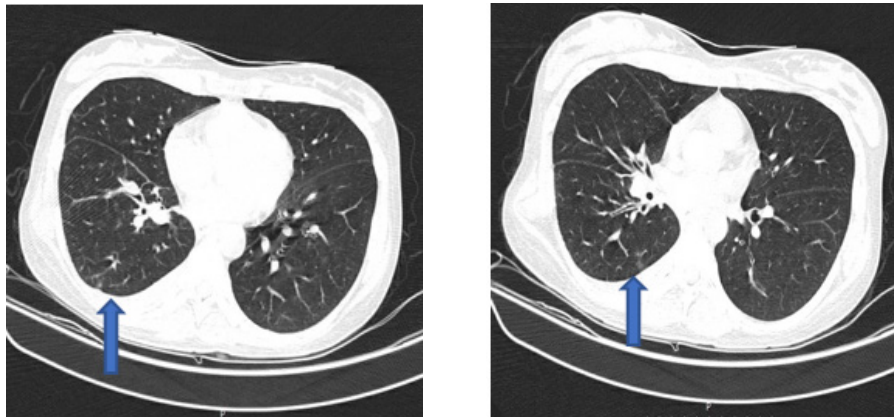
Fig.3(A, B): A normal chest spiral tomogram

A&B assays for *Clostridium difficile* were negative. A positive result of rt-PCR confirmed the diagnosis of COVID-19 in this patient with dominant gastrointestinal manifestations. Her drug history was positive for CellCept 1500 mg per day in divided doses, Prograf (tacrolimus) 4 mg per day in divided doses, prednisolone 10 mg per day, aspirin 80 mg daily, and required supplements. After discontinuation of CellCept and advice for the continuation of other therapies, the standard and accepted treatment for mild coronavirus infection, which was only hydration, antipyretics, and supportive care in addition to wide spectrum antibiotics due to suspicion of sepsis in an immunocompromised patient, were started. Ultrasonography revealed a decrease in kidney size and an increase in corticomedullary differentiation, indicating an episode of acute kidney injury. Ultrasonography of transplanted liver and Doppler study of hepatic vessels were all normal. During admission days, she continued to improve. She was discharged once she felt well.

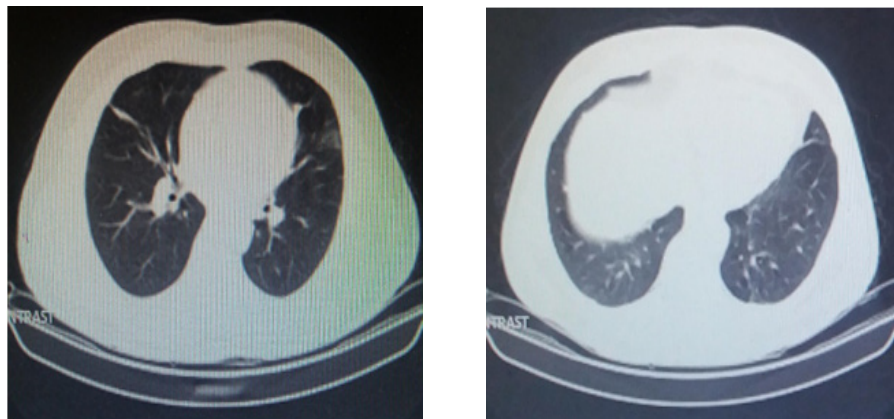
**Case-4:** A 33-year-old woman known case of liver transplantation due to primary sclerosing cholangitis (PSC) as a complication of ulcerative colitis (UC) since 8 years earlier, admitted with non-bloody diarrhea, nausea, weakness, and fever. On admission, she was conscious and oriented to time, place, and person. Her vital signs showed a mild tachycardia and a temperature of about 39°C. Although she did not have respiratory signs and symptoms, a lung spiral CT scan showed small multifocal patchy ground-glass opacities highly suggestive of COVID-19 along with a mild right pleural effusion (Figure 4). Finally, a positive rt-PCR for covid-19 confirmed the diagnosis. Ab-

dominopelvic ultrasonography and abdominal color Doppler sonography of the transplanted liver were unremarkable. Hematologic study and biochemical evaluation for liver function tests, serum bilirubin level, and kidney function tests were all within normal limits except for microcytic hypochromic anemia with serum iron profile compatible with iron deficiency anemia. Sepsis workups and secondary workups for opportunistic infections were negative. Besides post-transplantation medical therapies included tacrolimus 4 gr per day in divided doses, mycophenolate mofetil 2 gr daily in divided doses, prednisolone 5 mg daily, and aspirin 325 mg daily, she was on mesalamine 1 gr twice daily and ursodeoxycholic acid 300 mg thrice daily. Similar to previous cases presented in the study, immunosuppressant agents were continued except for mycophenolate mofetil. Hydration in addition to empiric antibiotic therapy for sepsis and hydroxychloroquine for coronavirus infection was started. After a long period of hospitalization, the patient was discharged after a significant improvement in clinical signs and symptoms.

**Case-5:** A 52-year-old man who underwent liver transplantation two years earlier due to NASH (Non-Alcoholic SteatoHepatitis) was admitted to the Emergency Department of Taleghani Hospital with non-bloody diarrhea, fever and chills, headache, nausea, vomiting, and abdominal pain. His medical history was notable for diabetes mellitus controlled by oral hypoglycemic agents. Ultrasonography of transplanted liver demonstrated fatty liver grade I and prominent intrahepatic ducts, especially in the left lobe. Doppler sonography of hepatic vessels was normal. The patient denied any respiratory symptoms. His spiral



**Fig.4(A, B):** Small multifocal patchy ground-glass opacities highly suggestive of COVID-19



**Fig.5(A, B):** Small multifocal ground glass in favor of coronavirus

CT scan of the chest revealed small multifocal ground glass in favor of coronavirus, and rt-PCR was positive for COVID-19 (Figure 5). Complete blood count and differentiation were within normal limits. A biochemical evaluation revealed serum AST and ALT near the upper limit of normal but a significantly elevated ALP of about 1000 IU/L, which gradually decreased during admission. Management of immunosuppressant agents was considered as previous cases by withholding CellCept, continuation of tacrolimus, and adjusting prednisolone. Due to its potential anti-coronavirus effects, sovodak (combination of sofosbuvir and daclatasvir) once daily for 5 days was started for the patient. He gradually improved and was finally discharged after a significant improvement in clinical signs and symptoms.

## DISCUSSION

Liver transplant recipients who are receiving immunosuppressive drugs are at a greater risk for be-

ing involved with a more severe form of the COVID disease. Above that, many symptoms in this group of patients may not be exhibited because of immunosuppressive drugs. On the other hand, we have to take into consideration that immunosuppressive drugs would modulate their immune system in response to coronavirus infection resulting in milder forms of the disease. As mentioned above, the presentation of this infection can be somehow complicated in liver transplant recipients.<sup>4</sup> In the study of Wu and colleagues and Richardson and co-workers, the case fatality rate was reported to be 12% among liver transplant recipients, which is somehow close to the results of hospitalized patients that were calculated about 17%.<sup>5,6</sup> In this study, risk factors that made liver transplant recipients more prone to death were male sex, lymphocytopenia, thrombocytopenia, longer time from transplantation, and presence of neoplasia.<sup>6</sup> On the other hand,

probable risk factors like hypertension, chronic kidney disease, diabetes mellitus, obesity, and peripheral/cardio/cerebrovascular diseases do not reach statistical significance as the cause of the more severe form of the disease among this group of patients.<sup>2</sup> These results are against the report of Huang and colleagues who presented a case of liver transplantation with the severe form of coronavirus infection unresponsive to antiretroviral therapies.<sup>7</sup> In contrast to the reports that present severe forms of coronavirus infection in immunosuppressed patients, there are some reports indicating fewer complications than the general population in liver transplanted patients may be in part due to the hyperinflammatory status of coronavirus infection, which is modulated by immunosuppression in this group of patients.<sup>8</sup> In the present study, a more severe form of the disease leading to death was seen in the second case, which was an Iranian man with liver transplantation due to cryptogenic cirrhosis without any other comorbidity. But the other cases had milder symptoms of coronavirus infection. Significant alterations in liver enzymes were not seen in our presented cases, which are in line with the results of Richardson and colleagues.<sup>2</sup> Immunosuppressant agents were adjusted for the patients in this study, so prednisolone, as well as tacrolimus, were continued and the stress dose was added to prednisolone. Cellcept was withheld. There are some studies indicating the fact that continuation or discontinuation of immunosuppressant agents does not affect the prognosis of liver transplanted patients.<sup>2</sup> A case of liver rejection was introduced by Zhong and colleagues after discontinuation of immunosuppressant agents.<sup>9</sup> Therefore, it is recommended by some authors that immunosuppression be continued for mild to moderate symptoms of coronavirus infection and be adjusted for patients with fever, lymphopenia, or acute respiratory distress syndrome (ARDS).<sup>10,11</sup> In the study of Lee and others, gastrointestinal symptoms were detected in 42% and 71% of those who were hospitalized. 8% of the patients had mild disease and the remaining patients

had equally moderate to severe disease. Hospitalized patients had comorbidities and were older.<sup>12</sup> In the study of Heimbach and colleagues, although an increased percentage of mechanical ventilation was reported among liver transplanted patients, mortality was detected significantly lower than the general population in this group of patients.<sup>12</sup> As reflected in the literature, the antipyretic of choice in these patients is acetaminophen,<sup>10</sup> which was used <3gr/day safely without any hepatic toxicity in our patients. There is not a unique consensus on the use of hydroxychloroquine and azithromycin in liver transplanted patients.<sup>10</sup> The presented cases in this study received hydroxychloroquine based on their signs and symptoms, but azithromycin, as well as kaletra (lopinavir/ritonavir) that their use was not supported by studies,<sup>10,11</sup> were not used. Sovadac (sofosbuvir/daclatasvir) that is still under controlled trials and has shown promising effects on decreasing the death toll from COVID-19 in hospitalized patients, was used in one of our patients.<sup>12</sup> As demonstrated in the study of Lee and colleagues, immunosuppressant agents were decreased but continued for these patients. In this situation, only 3 out of 27 hospitalized patients had elevations in liver enzymes up to 2-20 fold the upper limit of normal.<sup>13</sup> The overall percentage of death was reported 18% versus 29% in outpatient transplanted patients versus hospitalized patients, respectively.<sup>13</sup> Totally, the prognosis of coronavirus infection has not been worse than the general population in liver transplanted patients.<sup>14,15</sup>

#### ETHICAL APPROVAL

There is nothing to be declared.

#### CONFLICT OF INTEREST

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

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