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TRANSPLANT INFECTIOUS DISEASE

LETTER TO THE EDITOR

Successful deceased donor liver transplantation in candidates with high MELD and ongoing positive SARS-CoV-2 PCR

To the Editor,

At the onset of the coronavirus 2019 (COVID-19) pandemic, transplant centers worldwide reduced the number of transplants performed, due to uncertainties involving the safety and natural history of COVID-19 in recipients and donors and to ensure adequate resource allocation.[1] The management of liver transplant candidates with high Model for End-Stage Liver Disease (MELD) scores and COVID-19 infection is challenging, balancing risk of mortality without transplantation with uncertainties regarding prolonged viral shedding, optimal immunosuppression, and risk for progression of COVID-19.[2] Successful liver transplant after clearance of COVID-19 infection demonstrated by negative severe acute respiratory syndrome coronavirus 2019 (SARS-CoV-2) polymerase chain reaction (PCR) is reported.[3] Prior studies have found increased risk of mortality in the setting of symptomatic infection or preoperative COVID-19 infection less than 7 weeks prior to elective or emergent surgery, with at 3.6–4.1 times higher odds of death within 6 weeks of diagnosis.[4] However, delaying transplantation pending a negative test in patients with high MELD and prolonged active infection or viral shedding can risk increased mortality. The viral load in a patient's SARS-CoV-2 PCR test can be approximately quantified using the cycle threshold (Ct) value. Different reports suggest lower Ct values associated with higher viral load, viral recovery and more severe illness; therefore, this may aid in the pretransplant evaluation.[5,6] The values that have shown to not be associated with cell culture viral recovery or range from >24 (especially after 8 days from symptom onset) to 34.[5,7,8] We present two patients who underwent successful deceased donor liver transplantation (DDLT) with a positive SARS-CoV-2 nasopharyngeal PCR.

A 41-year-old female with ulcerative colitis on prednisone and cirrhosis secondary to primary sclerosing cholangitis was found to have SARS-CoV-2 on asymptomatic screening when admitted for decompensated cirrhosis and cholecystitis (Ct values: E: 20.6, N2: 22.9 on Cepheid Infinity platform). She had no evidence of airspace disease on chest computed tomography (CT) and nucleocapsid IgG was positive at day 20. Serial PCR on days 9–29 performed on the ABI 7500 (TaqPath COVID-19 Combo Kit), Cepheid Infinity (Xpert Xpress SARS-CoV-2), and Roche 6800 (Cobas SARS-CoV-2 Test) platforms were positive with Ct values increased to 31.5, 31.7 on the ABI 7500 instrument (Ct ≤ 37 positive) (Table 1A). Her initial MELD was 28 and increased to 40. After weighing the risks and benefits, she was listed for transplant on day 28 and underwent successful DDLT on day 35. High dose steroids and tacrolimus were used for immunosuppression. Mycophenolate was started on postoperative day 42 after 2 SARS-CoV-2 PCRs were negative. Allograft function remains normal at 5 months.

A 41-year-old male with alcoholic use disorder admitted for decompensated cirrhosis was found to have SARS-CoV-2 on asymptomatic screen (Ct ORF1ab: 32.9, N: 30.5). Chest radiography had no airspace disease and PCR at day 20 was negative. On day 31, he developed fever, cough, and hypoxia requiring supplemental oxygen and repeat SARS-CoV-2 PCR was positive (Ct ORF1ab: 14.7, N: 12.6, S: not detected) likely with the alpha variant (U.K./B.1.1.7), which produces a negative result for the S-gene target, though this could not be confirmed via sequencing. While we expect this to be a case of re-infection, it is possible that the initial positive test could have alternatively been a false positive. CT chest was consistent with COVID-19 pneumonia and convalescent plasma and dexamethasone were given with improvement. Remdesivir was not given initially due to hepatic failure. His MELD was 40 with a life expectancy of days. Repeat SARS-CoV-2 PCR at day 42 and 45 remained positive with increased Ct (ORF1ab: 23.9, N: 23.7) (Table1B). After weighing high risk of mortality without transplant and unknown risk with COVID-19, the patient was listed for transplant on day 44, received casirivimab/imdevimab on day 45, and underwent successful DDLT on day 47 with intravenous methylprednisolone and airborne precautions utilized in the operating room. Casirivimab/imdevimab was selected over convalescent plasma given its demonstration to reduce viral load and stronger evidence to reduce symptom duration, hospitalization and death.[9] He received remdesivir perioperatively. Postoperative course was complicated by bleeding requiring washout and delayed closure and cytomegalovirus viremia treated with ganciclovir. He received a regimen of steroids for immune suppression postoperatively, free of calcineurin inhibitor or anti-metabolite therapy. Repeat SARS-CoV-2 PCR was negative since day 66. The patient was ultimately discharged on day 120 with normal allograft function.

Liver transplantation in patients with COVID-19 is challenging due to risk for mortality without transplant and uncertainties regarding COVID-19, prolonged viral detection, and optimal posttransplant immunosuppression. Two patients with high MELD underwent successful DDLT with positive SARS-CoV-2 PCR. These represent very different case scenarios. The first patient was asymptomatic with possible evidence of viral shedding given the low Ct values. After evaluation for evidence of clinical disease, Ct values were helpful to guide decision making to proceed with transplantation, which was performed successfully once Ct was greater than 32. The second case represented

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TABLE 1 SARS-CoV-2 test results and cycle threshold

(A) Patient 1					
Hospital day	**Test platform**	**Result**	**ORF1ab**	**N gene**	**S gene**
0	Infinity[a]	Positive	NA	20.6	NA
9	Roche 6800	Positive	Unavailable	NA	NA
14	ABI 7500	Presumptive positive	ND	ND	34.7
23	ABI 7500	Positive	31.5	31.7	ND
29	ABI 7500	Positive	23.5	24.5	24.0
34	ABI 7500	Negative	ND	ND	ND
42	Roche 6800	Presumptive detection	Unavailable	NA	NA
49	ABI 7500	Negative	ND	ND	ND
51	Roche 6800	Negative	ND	NA	NA
(B) Patient 2					
Hospital day	**Test platform**	**Result**	**ORF1ab**	**N gene**	**S gene**
0	ABI 7500	Positive	32.9	30.5	ND
20	ABI 7500	Negative	ND	ND	ND
32	BioFire FilmArray	Positive	NA	NA	NA
34	ABI 7500	Positive	16.4	15.7	ND
42	ABI 7500	Positive	21.3	20.8	ND
45	ABI 7500	Positive	23.9	23.7	ND
53	ABI 7500	Positive	28.0	27.7	ND
59	ABI 7500	Positive	ND	30.0	ND
66	ABI 7500	Positive	ND	31.9	ND
81	ABI 7500	Negative	ND	ND	ND
95	ABI 7500	Negative	ND	ND	ND

SARS-CoV-2 tests performed on Patients 1 and 2 during hospital stay. For each test, the platform, result and cycle threshold (Ct) for each gene detected is shown. Gene targets that were not detected are listed as "ND," and gene targets that are not applicable to a given PCR test are listed as "NA." SARS-CoV-2 tests were performed using four different platforms: (1) ABI 7500 platform (ThermoFisher TaqPath COVID-19 Combo Kit, which detects ORF1ab, S, and N with Cts ≤37 defined as positive), (2) Cephied Infinity platform (Xpert Xpress SARS-CoV-2, which detects E and N2 and does not list specific Cts in their package insert to define a positive result), (3) Roche 6800 platform (cobas SARS-CoV-2 Test, which detects ORF1ab and E; the Ct values were not available to us for this study), and (4) BioFire Film Array which does not provide Ct values.

[a]For Infinity test performed at day 9, E gene was also detected at at Ct of 22.9.

a higher risk patient who was actively infected with a variant strain and radiographic evidence of COVID-19 pneumonia. Transplant was pursued once the patient was clinically improved and effectively treated with maximal therapy with rising Ct values. Although this patient was at a higher risk given recent active infection with low Ct and ongoing disease present, he successfully underwent DDLT given his high risk for mortality due to cirrhosis. Even though this patient had a good short-term outcome, the risk for patients to undergo transplant with more severe COVID-19 and active disease present despite up trending Ct values remains unknown as well as the risk to the health care system. For patients with lower Ct values or recent active disease, preoperative monoclonal antibody and perioperative remdesivir may assist in reducing risk for COVID-19 progression in the early posttransplant setting although more studies are needed to determine this. A combination of clinical factors and serial testing with cycle thresholds (Ct), an indirect marker of viral load, may be useful in assessing candidacy.[10,11]

The decision of the timing to pursue liver transplant in the setting of high MELD and recent COVID-19 infection remains complicated and requires careful pretransplant evaluation based on individual risk and benefit. While delaying surgery at least 7 weeks is preferred to minimize postoperative mortality and allow for conversion to negative PCR testing, this may not be feasible for patients awaiting liver transplantation who are at high risk for morality due to their underlying disease. These cases suggest that it is feasible to pursue DDLT at a shorter time interval depending on careful individual risk assessment and considering the limited resource of an organ.

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