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A Less Restrictive Policy for Liver Transplantation in Coronavirus Disease 2019 Positive Patients, Based Upon Cycle Threshold Values

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ABSTRACT

Coronavirus disease 2019 drastically impacted solid organ transplantation. Lacking scientific evidence, a very stringent but safer policy was imposed on liver transplantation (LT) early in the pandemic. Restrictive transplant guidelines must be reevaluated and adjusted as data become available. Before LT, the prevailing policy requires a negative severe acute respiratory syndrome coronavirus 2 real-time polymerase chain reaction (RT-PCR) of donors and recipients. Unfortunately, prolonged viral RNA shedding frequently hinders transplantation. Recent data reveal that positive test results for viral genome are frequently due to noninfectious and prolonged convalescent shedding of viral genome. Moreover, studies demonstrated that the cycle threshold of quantitative RT-PCR could be leveraged to inform clinical transplant decision-making. We present an evidence-adjusted and significantly less restrictive policy for LT, where risk tolerance is tiered to recipient acuity. In addition, we delineate the pretransplant clinical decision-making, intra- and postoperative management, and early outcome of 2 recipients of a liver graft performed while their RT-PCR of airway swabs remained positive. Convalescent positive RT-PCR results are common in the transplant arena, and the proposed policy permits reasonably safe LT in many circumstances.

THE SEVERE acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic has had an unprecedented and drastic impact on the solid organ transplant population worldwide [1]. Concerns include accepting transplantation donors and recipients with unrecognized SARS-CoV-2 infections, the impact of diminished post-transplant immunity on SARS-CoV-2 severity, and infection control.

At the onset of the pandemic, the absence of scientific evidence compelled transplant policymakers to impose stringent but safer policy for liver transplantation (LT). As such, the a priori approach for LT during the pandemic was delineated in a clinical algorithm that is primarily based on a binary positive or negative result of real-time quantitative reverse transcriptase polymerase chain reaction (RT-PCR) for the SARS-CoV-2 genome in airway samples [1,2], along with clinical and epidemiologic screening [1,2]. A recently updated approach requires, before organ retrieval, a negative SARS-CoV-2 RT-PCR respiratory specimen from donors previously known to have had coronavirus disease 2019 (COVID-19), unless >20 days from onset of symptoms to donation evaluation [3]. For recipients previously known to have had COVID-19, a negative RT-PCR is required within 24 hours of LT; if positive, LT should be deferred [4]. Restrictive transplant guidelines must, however, be reevaluated as data become available, and when supported by scientific evidence, less restrictive criteria are to be carefully considered and executed. Indeed, recent data show that 1. prolonged (up to 12 weeks) respiratory viral RNA shedding is common among adult patients, especially following severe illness [5,6]; 2. in some cases early convalescent negative results later became positive [7,8]; and 3. shedding of viral genome does not equate to infectivity, which depends on the replication capability of the virus [9–12]. In this this article

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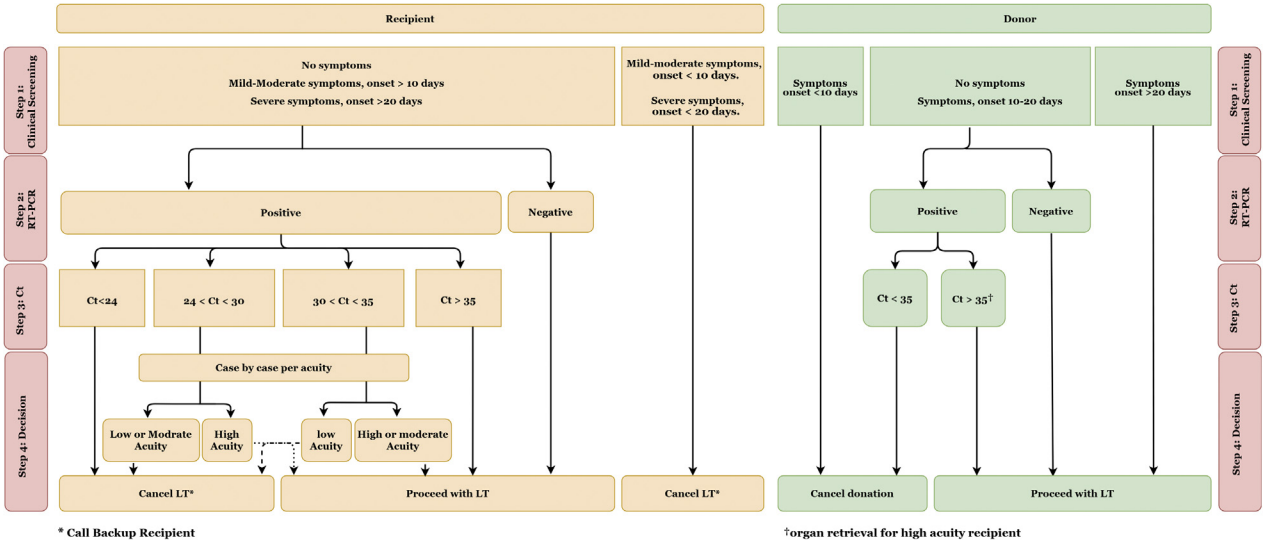

Fig 1. An algorithm for liver transplantation during the SARS-CoV-2 pandemic. The algorithm delineates evidence-based and less restrictive adjustments to previous transplant societies' recommendations and is centered on the severity of symptoms, days since onset of symptoms, and the cycle threshold of a positive RT-PCR of a respiratory specimen. Noninfectious shedding of viral genome occurs 10 and 20 days after mild-moderate and severe COVID-19 disease, respectively. Step 1: An asymptomatic candidate is one who lacks any clinical evidence suggestive of COVID-19 >21 days before screening. If symptomatic, days since onset of symptoms and disease severity should be determined. The candidate should have complete resolution of symptoms. Step 2: Some experts recommend 2 negative RT-PCR tests at least 24 hours apart for asymptomatic candidates due to the limited sensitivity (~70%) of each test [3,4]. Step 3: For RT-PCR targeting E, Nsp, or S genes, use Ct cut-off values of 24, 30, and 35. For RT-PCR targeting the N-gene or $ORF1_{ab}$-gene, use Ct cut-off values of 30, 32, 35, or 30, 33, 37, respectively. When Ct values of several genes are available, proceed with the safest value. Step 4: For recipients with a positive result, the decision whether to proceed with LT is case by case per acuity, as assessed by a transplant multidisciplinary panel. Risk-benefit should be discussed with the patient or proxy, and proper personal protective equipment should be donned during the peritransplant management. Organ retrieval from donors with Ct >35 should be considered for only high acuity recipients. Lower respiratory tract samples should be considered when there is a diagnostic uncertainty. Serology is not currently recommended to establish the absence of infectivity. COVID-19, coronavirus disease 2019; Ct, cycle threshold; LT, liver transplantation; RT-PCR, real-time quantitative reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. *Call backup recipient. †Organ retrieval for high acuity recipient.

we propose an evidence-adjusted and significantly less restrictive transplant policy for LT in RT-PCR–positive patients, based on scientific data gained this far in the pandemic (Fig 1). We introduce the proposed algorithm by delineating the pretransplant clinical decision-making, post-transplant immunosuppression and monitoring for SARS-CoV-2 infection, and early outcome of 2 LTs performed on recipients who recovered from a documented SARS-CoV-2 infection while airway swabs remained RT-PCR positive.

PATIENT 1

A 55-year-old man presented with pyogenic arthritis of a prosthetic knee was treated with 2 g of ceftriaxone intravenously daily for 6 weeks, during which acute on chronic liver failure developed (Table 1). Nasopharyngeal SARS-CoV-2 RT-PCR swabs on days 3 and 5 were negative, and he was listed for LT with a diagnosis of alcoholic cirrhosis. On day 9, a nasopharyngeal RT-PCR swab became positive with cycle threshold (Ct) of 14.6 and his listing was put on hold (status 7). Over the following weeks he developed respiratory distress, hemodynamic instability, and acute renal failure; he required respiratory support with high flow nasal cannula, vasopressors, and renal replacement therapy. Remdesivir was not given because of his severe liver disease. Subsequent weekly nasopharyngeal RT-PCR swabs remained positive with Ct values of 17.2, 24.6, and 25.3. SARS-CoV-2 IgG and total antibody, drawn 15 days after initial positive RT-PCR, were reactive (Fig 2). Given his critical condition, frailty, Model for End-Stage Liver Disease score of 40, and RT-PCR Ct greater than 24, the patient was cleared for a combined liver and kidney transplant 27 days after his initial positive RT-PCR. Transplantation, however, was delayed due to a superimposed *Burkholderia cepacia* pneumonia that necessitated initiation of mechanical ventilation, as well as vancomycin-resistant *Enterococcus faecium* bacteremia. LT from a SARS-CoV-2 RT-PCR–negative donor took place 53 and 6 days after his initial and most recent positive RT-PCR swab (Ct 14.6 and 35.1, respectively). Intraoperatively the patient received 500 mg of methylprednisolone. The kidney was grafted 2 days later. Post-LT immunosuppression included methylprednisolone and tacrolimus; a single dose of antithymocyte

globulin was added after his kidney transplant. The recipient had an adequate liver function but a delayed graft function of the kidney. His overall recovery was slow. Two nasopharyngeal RT-PCR swabs taken on postoperative days 9 and 20 were negative, and during his postoperative period, no clinical findings suggestive of an ongoing SARS-CoV-2 infection were found. All personnel involved in the intra- and postoperative care donned personal protective equipment and remained asymptomatic. SARS-COV-2 IgG and total antibody 66 days after initial positive RT-PCR were reactive.

PATIENT 2

A 37-year-old woman on the LT waitlist was admitted with fever, chills, cough, bilateral patchy opacities on chest x-ray, and with a SARS-CoV-2 RT-PCR–positive result from a nasopharyngeal swab with Ct value of 42. She did not require oxygen supplementation (Table 1). Her mycophenolate mofetil was held and her prednisone was increased to 10 mg daily. She was discharged home after 72 hours. A month later she had 2 negative SARS-CoV-2 RT-PCR results a week apart. She was admitted 94 days later for LT with a Model for End-Stage Liver Disease score of 23 and was found to have a positive nasopharyngeal SARS-CoV-2 RT-PCR with Ct of 39.9. SARS-COV-2 IgG and total antibody were reactive (Fig 2). The donor was SARS-CoV-2 negative. The patient received 500 mg of methylprednisolone intraoperatively; postoperative immunosuppression included methylprednisolone and tacrolimus. Two subsequent SARS-CoV-2 RT-PCR nasopharyngeal swabs were negative, and she was discharged home on post-transplant day 9. All personnel involved in the intra- and postoperative care donned personal protective equipment and remained asymptomatic.

Table 1. Preoperative Variables of Patients 1 and 2

	Patient 1	Patient 1
Age, y	55	37
Sex	Male	Female
Race	Hispanic	Hispanic
BMI, kg/m^2	47.5	25
MELD	40	23
Redo-transplantation, n%	no	no
Portal vein	Patent	Patent
TIPS	no	no
Etiology	Alcoholic	Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome
Associated HCC	no	no
Comorbidities	Hypertension, hypothyroidism, septic arthritis	none
Pretransplant RRT	Yes	No
Pretransplant hospitalization	Yes	no
Pretransplant ICU	Yes	No
Pretransplant vasopressors	Yes	No
Pretransplant intubation	Yes	0
Platelet count, $\times 10^9$/L	29	80
INR	2.4	1.7
Hematocrit, %	28.8	31
Bilirubin, mg/dL	3.2	16.4
Serum sodium, mmol/L	143	140
Creatinine, mg/dL	0.3	0.4
Albumin, g/dL	1.3	2.8
Glucose, mg/dL	83	114
White blood count, $\times 10^9$/L	5.4	6.7
Absolute lymphocyte, $\times 10^9$/L	0.1	0.4
Ct, lowest/ pretransplantation	14.6/35.1	42/39.9
Length of surgery, h	4.9	4.8
Blood product:		
pRBCs, units	27	3
FFP, units	27	6
Platelets, units	3	1
Cryoprecipitate, units	2	0
Donor age (y) and type	56/DCD	6/DBD

Abbreviations: BMI, body mass index; Ct, cycle threshold; DBD, donation after brain death; DCD, donation after circulatory death; FFP, fresh frozen plasma; HCC, hepatocellular carcinoma; ICU, intensive care unit; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PBC, primary biliary cirrhosis; pRBCs, packed red blood cells; RRT, renal replacement therapy; TIPS, transjugular intrahepatic portosystemic shunt.

DISCUSSION

Some data indicate that despite ongoing shedding of viral genome, persons with mild-to-moderate SARS-CoV-2 RT-PCR are usually noncontagious 8 to 10 days after onset of symptoms [9,10,12,13], and a replicable virus may be isolated up to 20 days after onset of symptoms in severe cases and in immunocompromised patients [12,14]. In addition, at least 16 studies established a strong correlation between isolating replicable virus and the viral genome load, as measured by log copies detected or its semiquantitative proxy—Ct value [8,9,13,15–26]. A 10-fold decrease in target gene copies corresponds to a 3.3 increase in Ct [8,13,27]. Six studies reported Ct cut-off values denoting noninfectious shedding and ranging 24 to 35 [13,17-19,21,23,26], and 4 additional studies identified Ct cut-off values, between 23 and >35, associated with low probability (<8.5%) for cultivable virus [15,20–22,25]. This expanding data indicate that clinical and transplant strategies regarding an ongoing SARS-CoV-2 infection or its infectivity are better informed via the Ct value. Moreover, safer, more refined, and less restrictive clinical decision-making is achieved when the Ct value is interpreted in the clinical context of days from symptom onset to test as well as illness severity [8,15,21,26]. A conceivably riskier approach is justified in high acuity recipients, similar to our patient 1, where LT is their ultima ratio [2]. Accordingly, the critically ill patient 1 was deemed

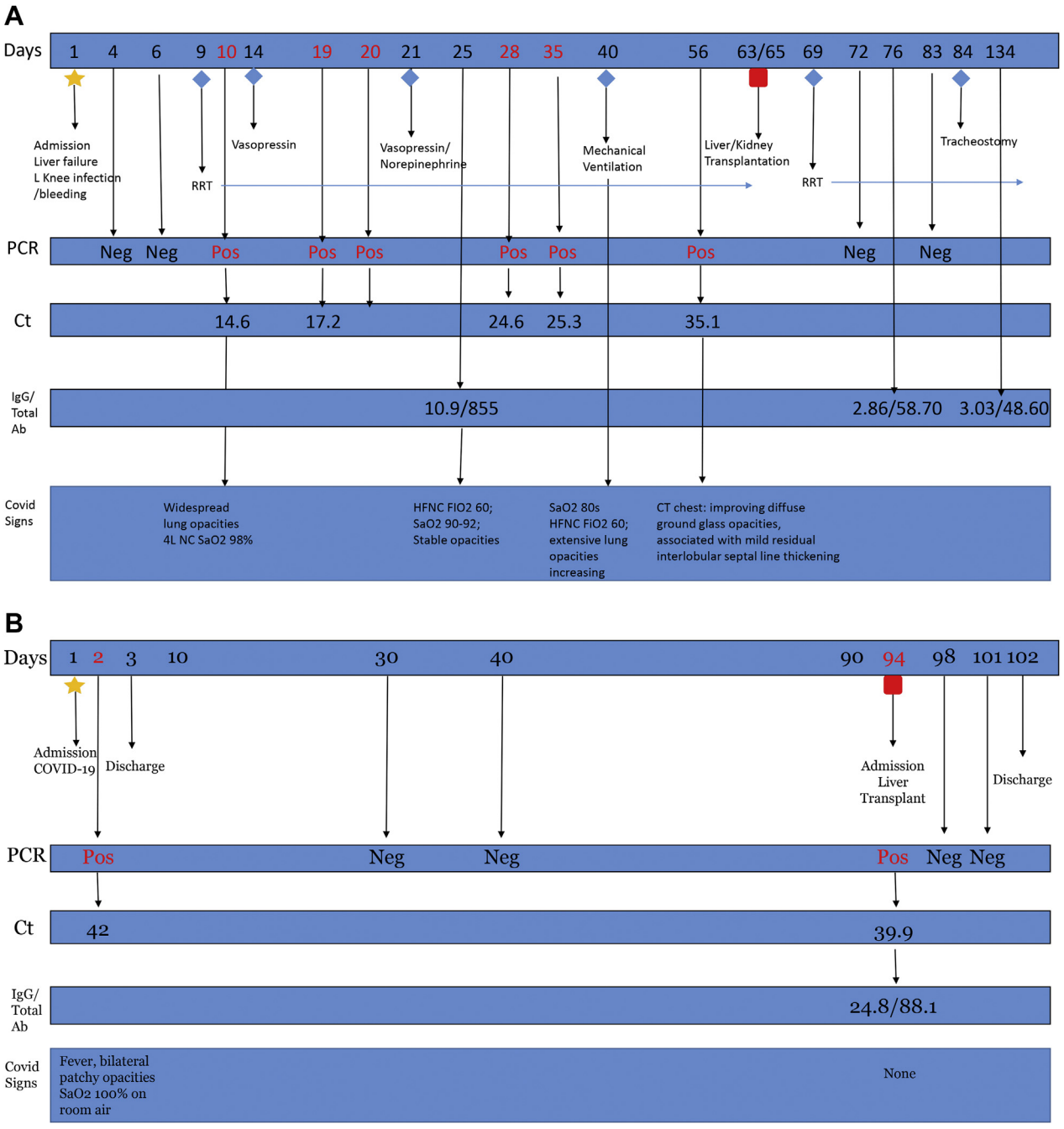

Fig 2. Timeline of liver transplantation and SARS-COV-2 infection. **(A)** and **(B)** display the peritransplant clinical events and SARS-COV-2 symptomatology and laboratory workup of patients 1 and 2, respectively. Antibody levels are expressed as S/Co ratio (normal 0-0.99). Ab, antibodies; COVID-19, coronavirus disease 2019; Ct, cycle threshold; CT, computerized tomography; FIO_2, fraction of inspired oxygen; HFNC, high-flow nasal canula; NC, nasal cannula; PCR, polymerase chain reaction; RRT, renal replacement therapy; SaO2, arterial oxygen saturation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

clear of an ongoing SARS-CoV-2 infection or infectivity preoperatively based on the clinical constellation of 1. 27 days since onset of symptoms; 2. improvement of his respiratory status; and 3. an increase in his Ct from 14 to 25 [13]. Likewise, a post-transplant reinfection [28] or exacerbation of an ongoing SARS-CoV-2 should be suspected when new pulmonary infiltrates are accompanied by inflammatory markers (eg, c-reactive protein, D-dimers, ferritin, or interleukin 6) [29], along with low or decreasing Ct values. On admission for LT, patient 2 was asymptomatic

but with a positive SARS-CoV-2 RT-PCR swab. Yet, despite having lower acuity end-stage liver disease, she was cleared for transplantation in view of her mild SARS-CoV-2 illness 94 days earlier and a Ct of 40. Serologic tests are helpful in cases with high clinical suspicion despite negative nucleic acid testing [30]. Although seroconversion may offer temporary immunity [31], serology is not currently recommended to establish absence of infectivity [4,12,30,32].

During the pandemic, our empirically modified post-LT immunosuppression induction regimen included steroids in lieu of antithymocyte globulin [33]. Both recipients received the modified regimen and did not appear to be negatively impacted by the prolonged shedding of viral genetic material. Undoubtedly, studies pursuing safe and efficacious regimens for induction of immunosuppression after solid organs transplant during this pandemic are necessary.

In light of the current resurgence of SARS-CoV-2 both worldwide and nationally, prolonged convalescent shedding of SARS-CoV-2 genome, in both recipients and donors, is becoming a common occurrence in the transplant arena. An evidence-adjusted algorithm for LT is presented in Fig 1. The new algorithm is guided primarily by Ct of RT-PCR and employs the previously proposed cut-off Ct values of 24 and 35, tiered to recipient acuity [8,13]. There remains a small but real risk of grafting a liver to a recipient with an ongoing SARS-CoV-2 infection, despite Ct value $\geq$24. Personal protective equipment should be donned during the perioperative management, and recipients should be monitored closely. Likewise, no Ct cut-off value uniformly predicts good outcomes. Several factors of specimen collection and handling impact the RT-PCR detectable viral RNA. SARS-CoV-2 Ct values may vary considerably between and within platforms, laboratories, and target genes [34]. Published Ct values should be compared with local RT-PCR assay reference values prior to clinical applicability [34,35]. Our results support the gradual implementation of less restrictive criteria for LT. The collection of additional data is recommended before the new policy is extended to transplantations of other organs, as these procedures mandate higher intensity post-transplant immunosuppression.

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