

Fatal COVID-19 in a Patient with End-Stage Liver Disease Wait-Listed for Liver Transplantation: An Evidence-Based Review of COVID-19 Screening Modalities Prior to Transplant

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Liver disease with elevated serum liver biochemistries occurs in 14% to 53% of hospitalized patients with coronavirus disease 2019 (COVID-19), and 6.6% of those hospitalized have underlying gastrointestinal or liver disease according to data from the US Centers for Disease Control and Prevention.¹⁻³ We present a patient on the liver transplant wait list with a Model for End-Stage Liver Disease–Sodium (MELD-Na) score of 37 who was asymptomatic 4 days prior to admission for

COVID-19 and who died after 11 days of hospitalization. Despite atypical symptom presentation, four organ offers were wisely declined while the COVID-19 nasopharyngeal swab polymerase chain reaction (PCR) test result was pending. COVID-19 screening of wait-list candidates who are imminent for liver transplantation may identify occult infection and prevent “close call” or “near-miss” situations that may lead to inadvertent transplant of COVID-19-infected patients.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; ESLD, end-stage liver disease; INR, international normalized ratio; LDH, lactate dehydrogenase; MELD-Na, Model for End-Stage Liver Disease–Sodium; N/A, not available; PCR, polymerase chain reaction; RdRp, RNA-dependent RNA polymerase; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell count.

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CASE REPORT

A 57-year-old African-American woman with end-stage liver disease (ESLD) due to nonalcoholic steatohepatitis who was wait-listed for transplant was admitted with 1 day of fatigue, nausea, and poor oral intake. Her ESLD was complicated by portal hypertension, hepatic encephalopathy, grade 1 esophageal varices, and recurrent ascites requiring remote transjugular intrahepatic portosystemic shunt placement. Four days prior to admission, she was seen in hepatology clinic without fever, respiratory, or gastrointestinal symptoms, at which time her MELD-Na score was 37. On admission, her temperature was 99.4°F, and she had stable chronic pancytopenia; total bilirubin was 20.9 mg/dL, which was stable from 1 week prior, but international normalized ratio (INR) had increased from 2.8 to 3.6 within a week. Chest radiograph did not reveal any consolidations. Examination was notable for mild hepatic encephalopathy, jaundice, and distended but nontender abdomen. Blood cultures were drawn and nasopharyngeal swab specimen for PCR did not detect influenza A/B or respiratory syncytial virus, but detected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA, which confirmed COVID-19. At the time of admission, the patient had been placed under contact and droplet conditions, and made status 7 on the liver transplant wait list.

On further interview, the patient reported that her sister, with whom she had close contact, had several weeks of intermittent dry cough. She was not currently working and denied recent travel. On day 2 of admission, the patient had a fever to 101.6°F but had an oxygen saturation of 98% on room air; repeat chest radiograph showed increasing left basilar opacity that progressed to bilateral multifocal patchy infiltrates the next day, and she now required 2 L supplemental oxygen through nasal cannula. Hydroxychloroquine 400 mg twice daily for two doses followed by 200 mg twice daily was started to complete a 5-day total course with careful electrocardiogram monitoring of QTc, which improved from 509 to 483 milliseconds after electrolyte repletion. On day 6 of hospitalization, she became more encephalopathic with increased work of breathing and hypoxia despite escalation in noninvasive respiratory support; she was subsequently intubated for acute respiratory distress syndrome and started on nor-epinephrine for vasopressor support. Azithromycin was started to complete a 3-day course given improvement in QTc to 450 milliseconds, and broad-spectrum antibiotics

TABLE 1. LABORATORY VALUES ON ADMISSION AND DURING HOSPITALIZATION

Laboratory Tests	On Admission	Peak or Nadir Values	Reference Range
White blood cell count ($10^3/\mu\text{L}$)	2.72	1.85	4.00-10.00
Hemoglobin	7.4	6.0	12.0-16.0 g/dL
Platelet count ($10^3/\mu\text{L}$)	31	16	150-399
Sodium level	139	134	137-147 mmol/L
Serum creatinine	1.53	4.06	0.65-1.00 mg/dL
Albumin level	3.0	2.4	3.5-5.0 g/dL
Total bilirubin	20.9	20.9	0.2-1.3 mg/dL
Alkaline phosphatase	82	87	30-125 U/L
AST	91	477	0-40 U/L
ALT	19	63	0-40 U/L
INR	3.62	4.00	0.83-1.23 seconds
Ferritin	1691	2429	12-260 ng/mL
D-dimer	13.26	13.26	0-0.6 mg/L
LDH	323	454	110-240 U/L
ESR	29	44	0-27 mm/hour
CRP	13.8	41.8	0-8.0 mg/L
Procalcitonin level	N/A	0.88	<0.10 ng/mL
Fibrinogen level	N/A	44	190-306 mg/dL
Creatine kinase	N/A	95	10-205 U/L

were started. Laboratory results were notable at this time for white blood cell count (WBC) of $10.11 \times 10^3/\mu\text{L}$, serum creatinine 2.08 mg/dL, total bilirubin 17.3 mg/dL, aspartate transaminase (AST) 113 U/L, alanine transaminase (ALT) 18 U/L, and albumin 2.5 g/dL. Ferritin level peaked at 2429 ng/mL, C-reactive protein (CRP) was elevated at 41.8 mg/L, erythrocyte sedimentation rate (ESR) was 44 mm/hour, lactate dehydrogenase (LDH) was 454 U/L, arterial lactic acid was 4.5 mmol/L, fibrinogen was 45 mg/dL, and creatine kinase (CK) was within normal limits. Over the ensuing days, the patient remained intubated with worsening hemodynamics and developed acute-on-chronic kidney injury and shock requiring multiple vasopressors (Table 1). After discussions of goals of care with the family, the patient was transitioned to comfort care and died on day 11 of hospitalization.

DISCUSSION

We report the case of a woman with ESLD who was wait listed for liver transplantation who presented with a 1-day history of fatigue, nausea, and poor oral intake, and was found to have COVID-19. She was seen in the outpatient clinic just 4 days prior to hospitalization and was asymptomatic. The case culminated in death from COVID-19 and highlights atypical and mild symptoms in some patients

with COVID-19 and underlines the importance of screening for COVID-19 in patients wait listed for transplant.

COVID-19 typically presents with fever, cough, and shortness of breath.^{4,5} However, patients can present with only atypical symptoms, which include chills, malaise, nausea, diarrhea, and abdominal pain in up to 8% of cases, and can be asymptomatic or presymptomatic in up to 56% of cases.^{6,7} Our patient presented with only fatigue, nausea, and poor oral intake in the setting of an already very high MELD-Na score. COVID-19 could have been overlooked if not for a high index of suspicion on the part of the transplant team. Due to a high MELD-Na score, there were four organ offers from the time of COVID-19 nasopharyngeal swab collection and positive PCR result, which were wisely declined. This “close call” or “near-miss” prompted the development of COVID-19 screening protocols in our center at a time when position papers recommending screening for COVID-19 had not yet discussed the merits and limitations of specific testing methodologies.⁸⁻¹⁰

A diagnosis of COVID-19 can be made by detection of SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab specimens.¹¹ Universal testing for COVID-19 using this method in women admitted for delivery in two large hospitals in New York City at around the peak of the pandemic showed that 13.7% were positive for SARS-CoV-2 but asymptomatic.¹² Similar results may be found in prospective transplant patients depending on their ability to shelter in place and avoid infection. However, the sensitivity of just one nasopharyngeal swab specimen tested for SARS-CoV-2 RNA by RT-PCR has been reported to be 88.6%.¹³ Repeat RT-PCR testing over several days was necessary to diagnose the rest of the cases and included repeat testing of nasopharyngeal swab specimens, as well as testing of sputum and stool. In another study, the highest positive rates for RT-PCR testing were found in bronchoalveolar lavage fluid specimens (93%), followed by sputum (72%), nasal swabs (63%), pharyngeal swabs (32%), stool (29%), and blood (1%).¹⁴ Although RT-PCR testing for COVID-19 remains a reference standard for diagnosis, serial testing of multiple specimens may be necessary to optimize sensitivity. Moreover, RT-PCR testing requires several hours of laboratory staff time, and results can be delayed for up to 2 days depending on laboratory staff workload.

Rapid molecular tests for COVID-19 are an option for diagnosis and may be a useful screening tool for patients whose transplant is imminent given their quicker turn-around

time.¹⁵ Open access data from the Centre for Evidence-Based Medicine at the University of Oxford suggest good sensitivity and specificity of rapid molecular tests according to preliminary data.¹⁵ At our center, ID NOW COVID-19 testing (Abbott Laboratories, Abbott Park, IL) based on nuclear acid amplification of the SARS-CoV-2 RNA-dependent RNA polymerase gene is available and can be used for screening. A negative result in an asymptomatic patient can be useful given its presumably high negative predictive value in patients with low pretest probability for infection. However, the performance characteristics of this and other rapid assays for COVID-19 need to be validated in large-scale real-world settings.

Adjunctive computed tomography (CT) scans of the chest could increase the sensitivity of COVID-19 case detection. In our patient, chest x-ray infiltrates developed only 2 days after admission. However, she would have likely had infiltrates detected had a chest CT been done.¹⁶ Typical chest CT findings in patients with COVID-19 include ground-glass opacities, multifocal patchy consolidation, and interstitial changes with a peripheral distribution.¹⁷ A study assessing the performance of chest CT in diagnosing COVID-19 showed that its sensitivity was 97% compared with positive RT-PCR results as the reference standard.¹⁸ Among patients with negative RT-PCR results and positive chest CT findings, 48% were considered as highly likely cases, and 33% were probable cases by comprehensive clinical review.¹⁸ In another study, all asymptomatic patients with known COVID-19 exposure who later had confirmed COVID-19 by RT-PCR testing had abnormal CT scan findings; in those who developed symptoms, the average number of days before symptom onset was 3 to 4 days.¹⁶ These data suggest that chest CT scans may be useful in identifying asymptomatic or presymptomatic COVID-19.

Our transplant center is located in Chicago, Illinois, and is a hot spot of COVID-19 in the United States. Given our high rates of COVID-19 despite stay-at-home orders from state government, we instituted COVID-19 screening guidance for patients admitted for liver transplantation based on currently available evidence. This includes symptom-based assessment prior to hospitalization by the primary transplant team, symptom-based assessment upon hospitalization by a transplant infectious disease physician and fellow, collection of a nasal swab specimen for rapid molecular testing, and a noncontrast chest CT scan (Fig. 1). We opted to use rapid molecular testing instead of RT-PCR because of its quick turnaround time and presumed high negative predictive value in an asymptomatic patient with

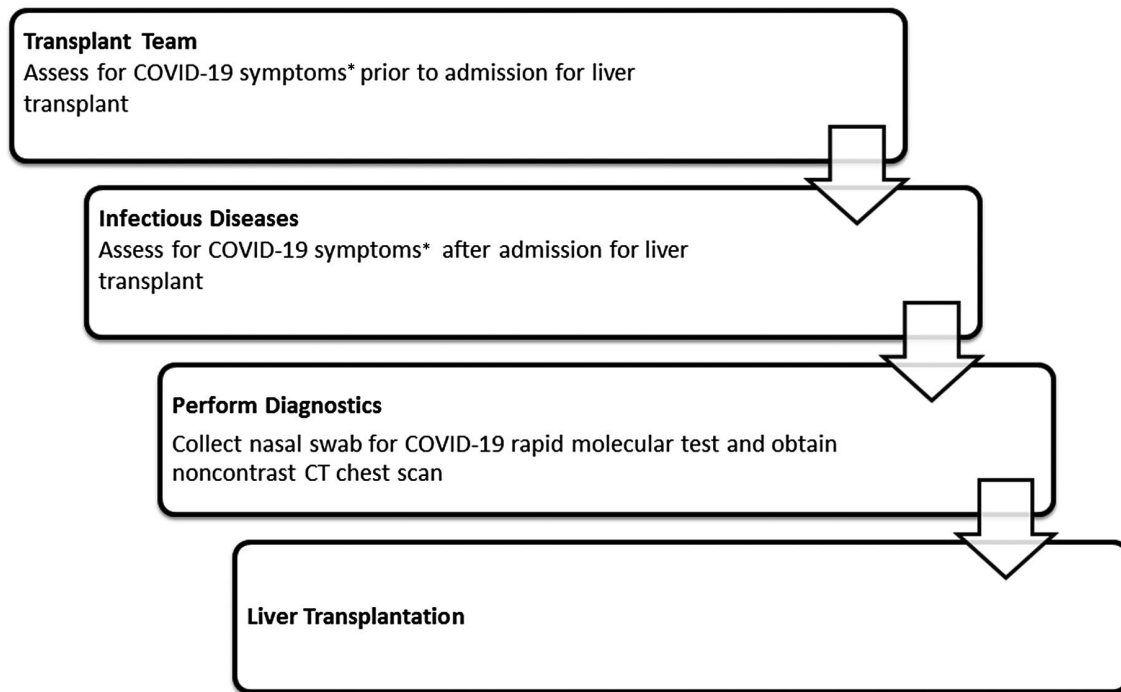


FIG 1 COVID-19 screening flowchart for high MELD-Na score liver transplant candidates. *Symptoms include fever, respiratory symptoms (cough, shortness of breath, sore throat, rhinorrhea), anosmia/ageusia, and/or diarrhea.

a normal chest CT and low pretest probability for infection. The absence of symptoms consistent with COVID-19, coupled with negative test results for both rapid molecular testing and chest CT, allows the team to pursue transplant and permits this life-saving procedure to occur in the midst of a pandemic.

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