



# DID THE COVID-19 PANDEMIC IMPACT LIVER TRANSPLANT PATIENTS?

Troupe Grimes MS2\*, Rajab Idriss, M.D.\*, Richard Trieu, M.D.®, Madhuri Mulekar, Ph.D.#, Phillip Henderson, D.O.\*, Pallavi A. Patil, M.D.‡

\*Departments of Gastroenterology and #Math & Statistics, University of South Alabama.

@-Department of Internal Medicine, University of Arizona. ‡-Department of Pathology, Baylor University Medical Center in Dallas and PathGroup.



## Introduction

Liver transplant patients are a unique population at high risk for opportunistic or viral infections due to chronic immunosuppressive therapy.<sup>1</sup> Additionally, angiotensin-converting enzyme 2 (ACE-2) receptors, which SARS-CoV-2 virus binds, are found in biliary and liver epithelial cells.<sup>2,3</sup> Due to the pandemic's morbidity and mortality risks on the general population, the aim of this study was to determine the impact of the COVID-19 pandemic on liver transplant patients. The objectives of the study were to determine percentage and severity of SARS-CoV-2 infections in this cohort, as well as the impact of the pandemic on medication compliance, graft survival, and overall survival.

## Methods and Materials

Liver transplant patients receiving post-operative care at a tertiary care center were included in this retrospective cohort study, approved by IRB. Relevant clinicopathological parameters before the pandemic and at most recent follow-up during the pandemic were studied by review of medical records. This included graft survival, patient survival, post-transplant complications, and pathology/radiology findings. Post-transplant complications were categorized as acute transplant rejection, chronic transplant rejection, biliary stricture, and hepatic artery stenosis. Pathology and radiology findings of fibrosis and steatosis were noted. In patients with positive SARS-CoV-2 test results, liver function tests including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and total bilirubin levels were recorded before and after infection.

Survey: An IRB-approved survey via telephone was conducted to supplement chart review. This allowed for further elaboration regarding COVID-19 testing, severity of infection, care received, medication compliance, and vaccination status. Statistical analysis: Data was analyzed using statistical software JMP 15.2.0. Results were considered significant at  $p < 0.05$ .

## Results

Of 193 patients, (61% males, 39% females), 15 tested SARS-CoV-2 positive (53% males, 47% females). Mild symptoms were reported in 53%, prolonged symptoms in 53%, hospitalization in 40%, and intensive care (ICU) admission in 7%.

## Results

Most common symptoms of COVID-19 experienced by patients included fatigue, dyspnea, fever, cough, and loss of taste and smell. The most common prolonged symptom was fatigue.

**Mortality:** Of the 13 total deaths in the study cohort, none were caused by COVID-19. Race, age at liver transplantation, indication for transplant, compliance to medications, and body mass index did not differ in SARS-CoV-2 positive and negative.

**Telephone Survey:** 135 patients and/or next of kin were successfully contacted, with 121 participating and 14 declining. Among participants, 93 had received at least 1 dose of a COVID-19 vaccine, while 28 were unvaccinated.

**Pathology and Radiology:** There were 56 biopsies and 51 radiology reports related to steatosis and fibrosis. Among these reports, there were 35 cases of steatosis, ranging from minimal to severe and 35 cases of fibrosis, ranging from portal fibrosis to cirrhosis. None of the COVID-19 patients underwent liver biopsy after infection.

**Medication Compliance:** For 91.67% of patients, compliance status remained the same before and during the pandemic. The likelihood of remaining compliant during the pandemic was greater for those who were compliant before than those who were non-compliant (Fisher's test,  $p < 0.0001$ ).

**Complications:** Regarding post-transplant complications, there was no difference in acute rejection, chronic rejection, and biliary stricture before and during the pandemic. However, probability for hepatic artery stenosis was greater before the pandemic ( $p = 0.0497$ ).

**Prognosis:** Overall survival at 1-, 3-, and 5-year for patients not tested for COVID-19 (85, 66 and 50 months respectively) was higher than those negative (80, 51 and 36 months respectively) ( $p < 0.01$ ).

**Table 1: Majority of patients receiving post-operative care, as well as testing positive for COVID-19, were White and male.**

Table 1: Demographics		Total Patient Population		COVID-19 Cases	
		N	% Total	N	% Total
Gender	Total	193		15	
	Male	118	61.1%	8	53.3%
	Female	75	38.9%	7	46.7%
Race	Total	193		15	
	White	163	84.5%	12	80%
	Black	20	10.4%	1	6.7%
	Other	10	5.2%	2	13.3%

**Table 2: SARS-CoV-2 positive cases symptoms and complications**

Table 2: SARS-CoV-2 positive	% (n/N)
Total positive	8 (15/193)
None or mild Symptoms	53 (8/15)
Hospitalization	40 (6/15)
ICU Admission	7 (1/15)
Mortality	0 (0/15)
Prolonged symptoms	53 (8/15)

**Table 3: Variation in survival times differed significantly by SARS-CoV-2 test group**

Table 3	Status of Test for SARS-CoV-2	N	Mean	Std Dev	Min	Max	P ANOVA
Age at liver transplant (years)	Negative	92	53.588	15.087	0.13	71.00	0.8326
	Positive	15	52.733	18.313	5.00	76.00	
	Not tested	86	52.217	14.620	0.67	69.00	
BMI	Negative	92	29.796	6.337	15.7	48.4	0.6248
	Positive	15	28.180	4.238	21.4	35.3	
	Not tested	85	29.420	6.032	17.9	50.1	
Total years of graft survival	Negative	92	6.50	6.77	1.0	31.0	0.0146
	Positive	15	8.27	5.81	2.0	21.0	
	Not tested	86	9.79	7.45	1.0	31.0	

**Table 4: SARS-CoV-2 positive cases liver enzymes before (pre) and after (post) testing positive**

Table 4:	N	Mean	Std Dev	Min	Max	Mean Diff (Post-Pre)	Std Err	P (paired t test) 2-sided test
Pre-ALP enzyme (IU/L)	14	104.43	45.99	35	192	52.25	15.63	0.0124
Post-ALP enzyme (IU/L)	8	161.38	80.74	85	278			
Pre-ALT enzyme (IU/L)	14	27.71	22.37	10	92	23.88	10.07	0.0495
Post-ALT enzyme (IU/L)	8	44.00	31.51	25	118			
Pre-AST enzyme (IU/L)	14	23.64	11.21	11	44	24.25	16.90	0.1943
Post-AST enzyme (IU/L)	8	46.38	51.80	13	172			
Pre-Total Bilirubin (mg/dL)	14	0.61	0.29	0.3	1.4	0.125	0.124	0.3454
Post-Total Bilirubin (mg/dL)	8	0.61	0.38	0.2	1.4			

## Discussion

There are conflicting reports in the literature about COVID-19 related morbidity and mortality in liver transplant patients. Among patients with COVID-19, a multicenter, international study found that liver transplant patients were significantly more likely to require ICU admission and invasive ventilation than their non-transplant counterparts.<sup>4,5</sup> Another study indicates lower mortality rates due to COVID-19 in liver transplant cohorts than the general population.<sup>6</sup> The COVID-19 pandemic did not affect mortality in our cohort. Our study reports lower ICU admission and mortality (6.7% and 0%) compared to other studies (10 to 33% and 12 to 18% respectively).<sup>4</sup> A possible reason could be immunosuppressive drugs reducing severe damage related to inflammatory response.

Patients who underwent testing for COVID-19 for various reasons and were found to have lower survival maybe associated with testing performed for hospital visits for symptoms/complications related to liver transplant follow-up.

ALP and ALT enzymes were elevated after SARS-CoV-2 infection, a finding supported by review of the current literature.<sup>7</sup> These liver enzyme elevations may be secondary to drug-induced liver injury related to treatment for COVID-19 or systemic inflammation due to infection.

## Conclusions

- The COVID-19 pandemic did not affect compliance nor mortality.
  - This finding supports reduction of immunosuppression is not needed and will help to mitigate fear of the pandemic among patients, towards maintaining better compliance
- ALP and ALT enzymes were elevated after SARS-CoV-2 infection in some cases that may be secondary to drug-induced liver injury or systemic inflammation.

## Contact

Pallavi A. Patil MD  
Baylor University Medical Center Department of Pathology  
Email: pallavi.patil@bswhealth.org  
Phone: 214-820-2251

Philip K. Henderson DO  
USA Health  
Email: pkhenderson@health.southalabama.edu  
Phone: 251-660-5555

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