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Original Article

Impact of COVID-19 on Liver Transplant Activity in the USA: Variation by Etiology and Cirrhosis Complications

Yong-Fang Kuo[1*], Paul Kwo[2], Robert J Wong[2] and Ashwani K. Singal[3,4*]

[1]Department of Biostatistics, University of Texas Medical Branch, Galveston, TX, USA; [2]Division of Gastroenterology and Hepatology, Veterans Affairs Palo Alto Healthcare System, Stanford University School of Medicine, Palo Alto, CA, USA; [3]University of South Dakota Sanford, School of Medicine, Vermillion, SD, USA; [4]Avera Transplant Institute, Sioux Falls, SD, USA

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Abstract

Background and Aims: The COVID-19 pandemic has impacted the care of patients with liver disease. We examined impact of COVID-19 on liver transplant (LT) activity in the USA. ***Methods:*** LT listings in the United Network for Organ Sharing (UNOS) database (April 2018–May 2021) were analyzed to examine the impact of COVID-19 pandemic on the LT activity based on etiology: hepatitis C virus (HCV), alcohol-associated liver disease (ALD), alcoholic hepatitis (AH), and nonalcoholic steatohepatitis (NASH) complications: hepatocellular carcinoma (HCC) and acute-on-chronic liver failure (ACLF) grade 2 or 3) and Model for End-Stage Liver Disease (MELD) score. Joinpoint regression models assessed time trend changes on a log scale. ***Results:*** Of 23,871 recipients (8,995 in the COVID era, April 2018–February 2020), mean age 52 years, 62% men, 61% Caucasian, 32% ALD, 15% HCC, 30% ACLF grades 2–3, and mean MELD score 20.5), monthly LT changes were a decrease of 3.4% for overall LTs and 22% for HCC after September 2020, and increase of 4.5% for ALD since 11/2020 and 17% since 03/2021 for ACLF grade 2–3. Monthly MELD scores increased by 0.7 and 0.36 after June 2020 for HCV and HCC respectively. ***Conclusions:*** The COVID-19 pandemic has impacted LT activity, with a decrease of LTs especially for HCC, and an increase of LTs for ALD and severe ACLF. Strategies are needed to reorganize cirrhosis patients to overcome the aftereffects of COVID-19 pandemic.

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Keywords: COVID-19; UNOS; OLT; Region; Public policies.

Abbreviations: ACLF, acute on chronic liver failure; COVID-19, coronavirus disease 2019; LT, liver transplantation; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

[*]**Correspondence to:** Ashwani K. Singal, University of South Dakota Sanford, School of Medicine, Avera McKennan University Hospital and Avera Transplant Institute, Sioux Falls, SD 57105, USA. ORCID: https://orcid.org/0000-0003-1207-3998. Tel: +1-605-322-8535 (office) and +1-605-322-5989 (research), Fax: +1-605-322-8536, E-mail: ashwanisingal.com@gmail.com; Yong-Fang Kuo, University of Texas Medical Branch, Galveston, TX 77755, USA. ORCID: https://orcid.org/0000-0003-1927-0927. Tel: +1-409-772-5276, Fax: +1-409-772-9127, E-mail: yokuo@utmb.edu

Introduction

Coronavirus disease 2019 (COVID-19) infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected normal life worldwide since the first case was reported in December 2019.[1–4] Because it is highly transmissible from person to person, COVID-19 has spread all over the world rapidly and was declared a pandemic in March 2020. Currently, this disease has led to over 809,300 deaths in the United States and 5.40 million deaths worldwide from the beginning of the pandemic to December 24, 2021 (www.cdc.gov).

Hospital resources needed to be prioritized worldwide in order to take care of the increasing patient load and hospitalizations of patients infected with SARS-CoV-2 and also to reduce transmission of the virus. Diversion of manpower and resources to take care of patients with severe COVID-19 infection, shortage of hospital and intensive care unit beds, limited availability of donor organs, and concern for risk of perioperative transmission, impacted routine care of patients with cirrhosis. Liver transplant (LT) activity has been impacted, limiting LT for urgent cases with acute-on-chronic liver failure (ACLF) and multiorgan failure, and delaying LTs for stable patients with lower model for end-stage liver disease (MELD) scores or with hepatocellular carcinoma (HCC).[5–8] The American Association for Study of Liver Disease recommended center specific policies on LT evaluations and activity during the COVID-19 pandemic as basis for mitigating the impact of COVID-19 on patients and healthcare providers.[9] In addition, shelter in place orders and depression/anxiety during the pandemic resulted in increased sales of alcohol beverages and increased alcohol consumption.[10,11] Clearly, this impacted patients with alcohol-associated liver disease (ALD), the leading indication for LT in the USA. With continuing increase in the COVID-19 case load in spite of availability of effective vaccines since December 2020, the impact of COVID-19 on LT activity in the USA needs to be explored further. The specific aims of this study were to examine the impact of COVID-19 on the LT frequency and variation in liver disease etiology, MELD score, and complications of cirrhosis, especially HCC or ACLF.

Methods

The United Network for Organ Sharing (UNOS) database

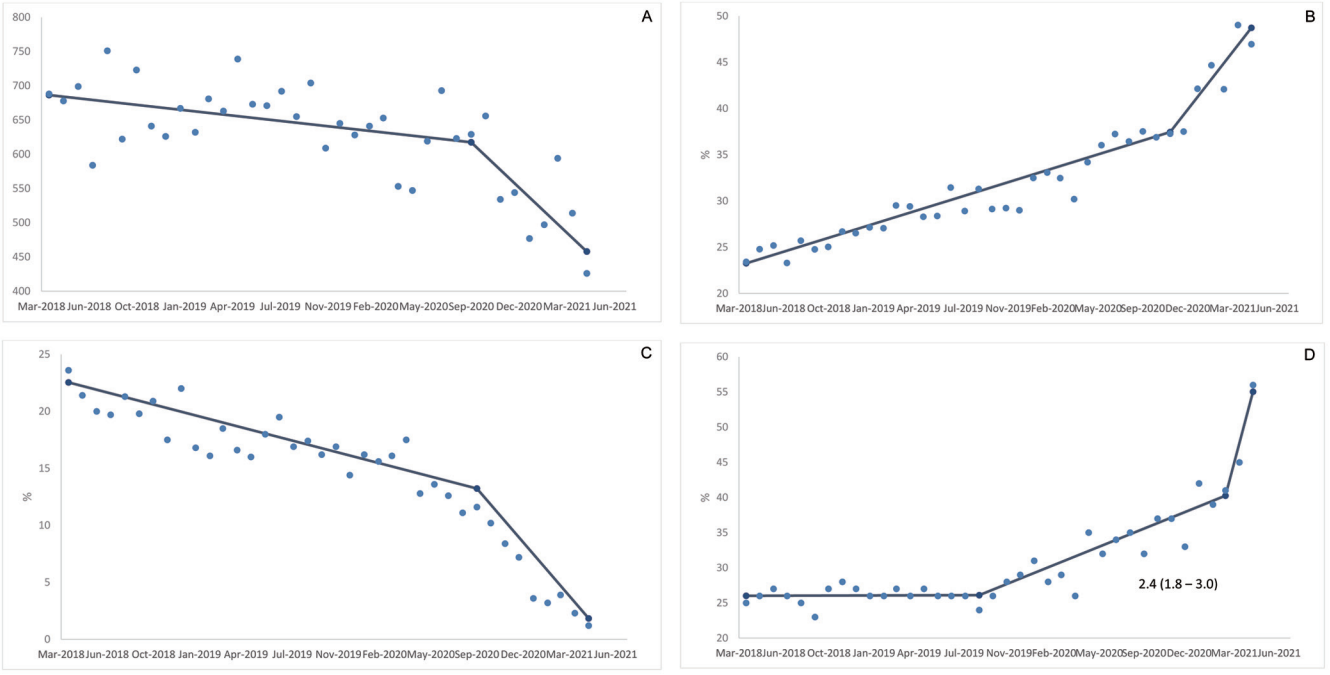

Fig. 1. Joinpoints in trends of monthly liver transplants from April 2018 to May 2021. (A–D) Total number of transplants (A), percent liver transplants for alcohol-associated liver disease (B), percent liver transplants for concomitant hepatocellular carcinoma (C), and percent liver transplants for patients complicated by acute on chronic liver grade 2 or 3 (D). The slope with 95% confidence interval indicates the monthly percentage change on a log scale before and after joinpoint.

was used for this study. As the COVID-19 infection was declared a pandemic in March 2020, LT listings were stratified to March 2020–May 2021 (COVID era) and April 2018–February 2020 (pre-COVID era). Given that there were etiological based changes in trends of LT even before the COVID era because of a decrease in HCV and increase in NASH and ALD transplants, we purposely examined trends over 22 months in the pre-COVID era so that we could have a stable trend during that period, which we then compared with the change in trend during COVID era. The number of LTs in each month from April 2018 to May 2021 were counted and the percentage and standard error (SE) of LTs by month were calculated for liver disease etiology, including hepatitis C virus infection (HCV), ALD, nonalcoholic steatohepatitis (NASH), and alcoholic hepatitis (AH), and for cirrhosis complications of HCC and grades 2 and 3 ACLF. ACLF and its grades were determined as published earlier based on EASL-CLIF criteria (Supplementary Table 1).[12] The average and SE of the MELD scores for each of the above etiologies by month were calculated. The monthly statistics were plotted, and joinpoint regression models, with a maximum of five possible joinpoints, were used to assess whether time the trend had significant changes. A sequential application of the permutation test using 4,500 possible randomly permuted datasets and the Bayesian Information Criterion were used to determine the optimal number of joinpoints. The statistical analysis was conducted with SAS version 9.4 and joinpoint Regression Program, Version 4.9.0.0 (https://surveillance.cancer.gov/joinpoint/).

Results

Frequency of all transplants

A total of 23,871 LTs (mean age 52 years, 62% men, 61% Caucasian, 32% ALD, 15% HCC, 30% ACLF grade 2–3, and mean MELD score of 20.5) were performed during the study period. Of all the LTs, 15,312 were performed before COVID-19 was declared a pandemic (April 2018–February 2020) and 8,995 were performed between March 2020 and May 2021. Analysis of the monthly frequencies of LT during the study period showed an effect of COVID-19 infection, with a joinpoint in September 2020 (Fig. 1A). The analysis showed a 3.4% (95% CI: 1.3–5.4%) monthly decrease in the number of LTs performed on a log scale between September 2020 and May 2021. We also compared the 3-month post-transplant patient survival in the pre- and post-COVID eras. Overall survival was 96.2% at 3 months after liver transplantation without any joinpoints throughout the study period.

Frequency of transplants for HCV, ALD, and NASH

Of the 23,871 LT during the study period, 7,536 (31.6%), 4,387 (18.4%), and 2,094 (8.8%) were performed for ALD, NASH, and HCV respectively. Analysis of the monthly frequency of LTs showed an effect of COVID-19 infection among the LTs for ALD, with a joinpoint in November 2020 (Fig. 1B). The analysis showed a 4.5% (95% CI: 2.4–6.6%) monthly increase in the percentage of LTs performed for ALD on a log scale between November 2020 and May 2021. Of 7,536 LTs for ALD during the study period, 1,528 performed after November 2020 were in younger, women who were less likely to have comorbid diabetes compared with 6,008 LTs for ALD between April 2018 and October 2020 (Table 1). LT performed for ALD after November 2020 were more likely to use a poorer quality organ, and more likely to have AH (10% vs. 6%), ACLF grade 2–3 (64% vs. 51%) and poor performance status (53% vs. 44%, Table 1). Although, there was a 4.2% monthly increase in LTs for AH by monthly throughout the study period, no joinpoint was

Table 1. Baseline characteristics comparing time periods based on joinpoint analysis of liver transplants (LTs) for hepatocellular carcinoma (HCC), acute on chronic liver failure (ACLF), and alcohol-associated liver disease (ALD) including alcoholic hepatitis (AH)

	LT for HCC (N=3,618)			LT for ACLF grade 2–3 (N=7,008)				LT for ALD (N=7,536)		
	04/18–08/20 (N=3,321)	09/20–05/21 (N=297)	P	04/18–08/19 (N=2,984)	09/19–02/21 (N=3,388)	03/21–05/21 (N=636)	P	04/18–10/20 (N=6,008)	11/20–05/21 (N=1,528)	P
Age (Mean, SD yrs.)	62.4, 7.3	61.7, 9	0.11	48.5, 17	48.7, 15	46.5, 15	<0.006	52, 10.5	49.5, 10.7	<0.001
% Males	77	75	0.44	59	59	58	0.68	72	69	0.018
% C, AA, H	58, 6, 29	57, 8, 29	0.45	53, 8, 32	55, 9, 31	58, 7, 30	0.034	67, 4, 27	67, 4, 25	0.14
BMI (Mean, SD)	29.6, 5.4	29.8, 5.7	0.61	28.5, 6.8	28.6, 6.8	28.9, 7	0.32	28.3, 5.7	28.1, 5.9	0.14
% Obesity	45	46	0.67	42	40	40	0.27	37	35	0.15
% DM	39	42	0.41	21	19	20	0.35	17	12	<0.001
% <HS, HS, College	8, 43, 49	6, 39, 55	0.076	7, 36, 57	6, 35, 59	3, 35, 62	<0.001	4, 36, 60	2, 36, 62	<0.003
% MC, MD, Pvt	66, 13, 51	36, 17, 47	0.14	18, 24, 58	16, 25, 59	13, 25, 62	<0.001	17, 23, 60	12, 24, 64	<0.001
% HCV, ALD, NASH	23, 9, 12	14, 12, 15	0.002	6, 38, 15	5, 48, 53	3, 53, 12	<0.001			
% Alcoholic hepatitis	0	0	NA	4.2	6.5	9.1	<0.001	6	9.8	<0.001
% ACLF (grade 2–3)	7.2 (3.3)	14.7 (5.5)	<0.001					51 (39)	64 (49)	<0.001
% Liver failure	2.7	3.4	0.47	69	72	76	<0.001	34	44	<0.001
% Kidney failure	5.5	8.4	0.042	66	67	67	0.95	35	45	<0.001
% Coagulation failure	4.4	9.4	<0.001	56	57	59	0.22	29	34	<0.001
% Brain failure	3.3	2	0.24	39	38	38	0.60	18	18	0.73
% Lung failure	0.03	0	0.76	10	10	9	0.43	2.9	2.4	0.32
% CV failure	1.3	0.5	0.33	35	29	25	<0.001	12	11	0.35
% Ascites	48	61	<0.001	87	88	87	0.70	89	92	<0.001
% HE grade 3–4	37	46	0.006	83	83	83	0.21	24	23	0.73
% SLK	2	2.7	0.41	12.1	10.7	10.5	0.11	8.1	8.8	0.42
% KPSS (80–100, 50–70, <50)	45, 49, 6	43, 48, 9	0.40	7, 28, 65	8, 23, 69	8, 20, 72	<0.001	14, 42, 44	11, 36, 53	<0.001
SC (Mean, SD)	1.04, 0.7	1.18, 1.08	<0.002	2.2, 1.7	2.2, 1.7	2.17, 1.7	0.62	1.76, 1.47	1.93, 1.54	<0.001
SB (Mean, SD)	2.4, 3.8	2.8, 3.9	0.055	19.7, 13.1	20.5, 13	21, 12.4	0.012	11.6, 11.9	14, 11.9	<0.001
INR (Mean, SD)	1.44, 0.8	1.59, 0.69	<0.002	2.8, 1.5	2.9, 1.8	2.8, 1.3	0.24	2.2, 1.1	2.3, 1.0	<0.001
MELD-Na (Mean, SD)	13.7, 7.3	15.8, 7.8	<0.001	35.8, 7.5	36.4, 6.8	36.5, 6.2	0.001	28.3, 9.6	30.9, 8.3	<0.001
Waiting (Mean, SD)	269, 157	130, 82	<0.001	63, 136	29, 70	9, 13	<0.001	78, 131	21, 32	<0.001
% HCV NAT + donor	6.8	5.5	0.41	2.8	4	4.5	0.014	5.1	5	0.86
DRI (Mean, SD)	1.64, 0.40	1.75, 0.41	<0.001	1.57, 0.4	1.62, 0.39	1.61, 0.37	<0.001	1.59, 0.37	1.63, 0.36	<0.001

SD, standard deviation; C, Caucasian; AA, African American; H, Hispanic; HS, high school; MC, Medicare; MD, Medicaid; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; HE, hepatic encephalopathy; SLK, simultaneous liver kidney; KPSS, Karnofsky's performance status scale; SC, serum creatinine; SB, serum bilirubin; INR, international normalized ratio; MELD, Model for end-stage liver disease; DRI, donor risk index.

Table 2. Joinpoints in trends of monthly average MELD score among liver transplants between April 2018 and May 2021

Indication	Time period	Slope (standard error)*
Hepatitis C virus infection	Apr 2018–June 2020	0.05 (0.031)
	June 2020–May 2021	0.70 (0.170)*
Alcohol-associated liver disease	Apr 2018–Sep 2019	−0.02 (0.038)
	Sep 2019–May 2021	0.19 (0.025)*
Nonalcoholic steatohepatitis	Apr 2018–Oct 2019	−0.05 (0.040)
	Oct 2019–May 2021	0.17 (0.041)*
Acute on chronic liver failure grade 2 or 3	Apr 2018–May 2021	0.03 (0.007)*
Alcoholic hepatitis	Apr 2018–May 2021	−0.03 (0.034)
Hepatocellular carcinoma	Apr 2018–June 2020	0.03 (0.016)
	June 2020–May 2021	0.36 (0.130)*

Slope is expressed as monthly average MELD score change. For example 0.7 means monthly MELD score increase by 0.7. Rates that change at a constant percentage every month linearly on a log scale. *p<0.05. MELD, Model for end-stage liver disease.

observed. Similarly, there was no joinpoint for LTs for HCV, in which there was a linear decrease in LT of 2.5% (95% CI: 2.1–3.0%) on a log scale every month between April 2018 and May 2021. There was a joinpoint for related to NASH, it was prior to the COVID era in August 2019, with a 1.0% (95% CI: 0.0–2.0%) monthly decrease in the number of LTs for NASH between August 2019 and May 2021.

Analysis of the average monthly change in MELD scores during the study period showed an impact of COVID-19 era for HCV-related LTs, with a joinpoint in June 2020 (Table 2). The average MELD score increased by 0.7 (SE: 0.17) every month for HCV-related LTs between June 2020 and May 2021. Although, there were joinpoints in LTs for ALD and NASH, there was no impact in the COVID era, with joinpoints after September 2019 (average MELD score increase of 0.19, SE: 0.025)) and October 2019 (average MELD score increase of 0.17, SE: 0.041).

Frequency of transplants for cirrhosis complications: HCC or ACLF grades 2–3

Of 23,871 LT during the study period, 3,618 (15.2%) were performed for HCC and 7,008 (29.4%) for ACLF grade 2–3 (Table 1). Analysis of monthly frequencies of LTs for HCC showed an effect of COVID-19 infection, with a joinpoint in September 2020 (Fig. 1C). The analysis found a 22% (95% CI: 16.4–27.0%) monthly decrease on a log scale of LTs performed for HCC between September 2020 and May 2021. LT recipients for HCC after September 2020 (n=297) were more likely to be college graduates, with Medicaid insurance, with LTs for ALD-related ACLF, higher MELD scores and the use of poorer quality organs compared with 3,321 LTs for HCC performed between April 2018 and August 2020 (Table 1). Analysis of monthly frequencies of LT for ACLF grades 2–3 showed an effect of COVID-19 infection, with a joinpoint in March 2021 (Fig. 1D). The analysis showed a 17% (95% CI: 2.7–33.2%) monthly increase in LTs performed for ACLF grade 2–3 between March and May 2021. Another increase was observed, but it was before COVID-19 was declared a pandemic, with LTs for ACLF grade 2–3 increasing by 2.4% (95% CI: 1.8–3.0%) every month between September 2019 and February 2021. LTs performed for ACLF grade 2–3 after March 2021 (n=636) were younger, more likely to be graduates, with private insurance, and LTs because of ALD and/or AH, with higher MELD scores, and poorer quality organs compared with 3,388 LTs for ACLF grade 2–3 between September 2019 and February 2020 and 2,984 between April 2018 and August 2019 (Table 1). Analysis of the average monthly change in MELD score during the study period showed an impact of COVID-19 era for HCC-related LT, with a joinpoint in June 2020 (Table 2). The average MELD score increased by 0.36 (SE: 0.13) every month for HCC-related LTs between June 2020 and May 2021. Although, the average monthly MELD score increased by 0.03 (SE: 0.007) in LT recipients who were in ACLF grade 2–3, there was no joinpoint or impact of the COVID era.

Frequency of transplants for acute liver failure

A total of 3.2% of the LTs were performed for acute liver failure (UNOS codes 4100, 4101-4108, and 4110) without any joinpoint during the study period. Similarly, there were no joinpoints in any of the regions for LT performed for acute liver failure.

Discussion

The main findings of our study are that the COVID-19 pandemic was associated with a decrease in the number of LTs, especially for HCC, and an increase in the proportion of transplants for ALD and ACLF grades 2 and 3. In addition, the MELD scores of transplant candidates with HCV cirrhosis or HCC who received LTs were higher during the COVID-19 pandemic. In recent analyses using the UNOS database (June 2019 to February 2021), the number of listings and LTs remained unchanged in spite of an increase in ALD listings and LTs during the COVID-19 pandemic.[13–15] In another study using the UNOS database (January–June 2020) assessing 3,600 LT, a 38% decrease in the overall number of LTs during weeks 10–15 of 2020 was observed.[16] In an international study using the European and USA LT registries, the frequency of all solid organ transplants including LTs decreased during the first 3 months of the pandemic, stabilized after June 2020, and then decreased again between October and December 2020. We also found a decrease in the number of LTs starting in September 2020.[17] Shelter in place orders, impact on routine care of cirrhosis patients following the reduction in outpatient clinic visits, diverting resources and manpower to take care of increasing COVID-19 load, and reduction in organ donor availability during the COVID-19 pandemic explains the reduction in LT activity observed in our and other studies.[4,6–10]

ALD-related LT activity increased during the COVID-19

pandemic without any impact on HCV and NASH related LT. In a recent analysis using the UNOS database, COVID-19 era was associated with an increase in LTs for ALD by 10.7%, and the ALD etiology contributed to 40.1% of all LTs performed in the COVID era.[13] In another study reporting LT activity in a single tertiary care center between January 1 and August 25, 2020, a 62% increase in transfers for decompensated ALD patients was observed even during the declining COVID-19 period of April 23, 2020 to August 25, 2020. In this study, of the 30 patients with severe AH not responding to medical therapy, nine (16%) received an early LT, with about two LT per month for severe AH compared with one LT every 2 months at that center prior to the pandemic.[18] In another study using the UNOS database (March 2018 to February 2021), LTs for AH increased by 13.1 (SE: 4.3) every month starting June 2020.[15] Psychosocial stress resulting from direct and indirect effects of COVID-19, shelter in place orders, and increased alcohol sales during the pandemic leading to increasing alcohol consumption, and resulted in decompensation of cirrhosis and need for LT.[10,11] For example, of the nine patients at a single center who received an early LT for severe AH during the pandemic, pandemic-related stressors accounted for increasing alcohol use in three, with the death of a loved one, loneliness, and essential workers without enough protective equipment in one patient each.[18] We observed a continuous rise in LTs for severe AH after 2018, but no association with the COVID-19 era. Our analysis also found an impact of the COVID era on LTs performed in patients with grade 2 or 3 ACLF beginning in March 2021. This was associated with an ALD etiology, with 53% of transplants for grade 2 or 3 ACLF between March and May 2021 because of ALD compared with 38% before September 2019. Delay in cirrhosis care with reduced face-to-face clinic visits and increased prevalence of alcohol abuse during the COVID pandemic may account for a delay in presentation of patients with ACLF who needed LT as a salvage therapy.[19,20] In our analysis, the MELD score had to be higher in our analysis in order to receive an LT for HCC during the COVID-19 pandemic. A Markov model based on a 50% reduction in organ donor availability during the COVID-19 pandemic in Italian wait-listed patients for T2 HCC showed a net benefit of LT starting at a MELD score of 30 compared with 15 before the COVID-19 pandemic. The authors suggested that LT for HCC should focus on T2 HCC patients who have the highest net survival benefit.[21]

The strengths of our study were extending the period of analysis until May 2021 and comparing the COVID period with a 2-year pre COVID period ending in March 2018. Further, our statistical analysis used joinpoints to find the best fitting log linear regression model from data compared with previous analyses with a specified fixed joinpoint of Apr 2020. It would have been interesting to include donor and recipient SARA-COV2 PCR data, but that was not available in the UNOS dataset. We do acknowledge the limitations of our retrospective cohort design. The monthly frequency analysis did not provide a large enough sample size to test the association of shelter in place orders with state-level and center-level variation in LT activity. We also acknowledge that the change in organ allocation in February 2020 with capping of MELD exception points for HCC-related listings may have contributed to some of the changes observed in our analysis, especially in the decrease of HCC-related LTs.

In conclusion, the COVID-19 pandemic was associated with a decrease in number of LTs especially for concomitant HCC, and an increase in the proportion of transplants for ALD and grade 2 and 3. ACLF. In addition, the MELD score had to be higher during the COVID-19 pandemic in order for patients with liver disease caused by HCV and those with HCC to receive an LT. The delay in cirrhosis care, increased alcohol use during the pandemic as a result of shelter in place orders and the subsequent increase in increasing life stressors continue to impact cirrhosis patients. Strategies are needed to reorganize these patients in the community as a basis for coming out of the aftereffects of pandemic of COVID-19.

Funding

None to declare.

Conflict of interest

AKS has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Concept and design (AKS, YFK), experiments and procedures (YFK), data interpretation (AKS, YFK, PK), writing the article draft (AKS, YFK). All the authors reviewed, provided intellectual input, and approved the final version.

Data sharing statement

The data used to support findings of the study are available in the publicly available UNOS dataset.

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