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Article type : Editorial

With Alcohol as the fuel, COVID is the match: Liver Transplantation for Alcoholic liver disease is increasing in the United States

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/HEP.32141](https://doi.org/10.1002/HEP.32141)

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Abbreviations

AH	Alcoholic hepatitis
ALD	Alcoholic liver disease
HCV	Hepatitis C Virus
NAFLD	Non-alcoholic fatty liver disease
LT	Liver transplant
MELD	Model for End Stage Liver Disease
SUD	Substance use disorder

In this issue, Cholankeril et al demonstrate a clear and convincing increase in listing and transplantation for alcohol-associated liver disease (ALD) in the United States that coincides with the onset of the COVID pandemic.(1) Even before the pandemic, the global burden of ALD was heavy and increasing. In the US, the 12-month prevalence of alcohol use disorder prior to COVID was at least 13.9% and most commonly observed in young, male patients but with rising rates in women as well.(2) In 2012, the mortality attributed to ALD was nearly 20,000 deaths per year with many due to alcoholic hepatitis (AH).(3) The COVID pandemic led to many abrupt and substantial changes in healthcare including decreased access to providers (including substance use disorder [SUD] therapists and support groups), high rates of unemployment, increased social isolation, and global uncertainty and fear that precipitated a national mental health crisis. These stressors also increased alcohol use and binge-drinking, which were exacerbated during lockdowns.(4,5) For example, every 1 week in time spent at home during the COVID lockdown led to a 19% increase in binge drinking. This trend coupled with the ubiquitous availability of inexpensive alcohol led to a national increase in alcoholic beverage sales in the United States of 55% in 2020 alone along with an alarming 243% increase in on-line sales compared to 2019.(6)

In the current study, the month-to-month listing and transplantation rates in the pre-COVID era (1/16-3/20) were compared to the COVID era (4/20-3/21). Although overall rates of listing and transplantation were unchanged, the rate of ALD specific listing (+7.26%, $P<0.001$) and transplantation (+10.67%, $P<0.001$) markedly increased and accelerated beyond projections (**Figure 1**). Simultaneously, wait-listing

for hepatitis C virus (HCV) and non-alcoholic fatty liver disease (NAFLD) significantly dropped. While HCV listings were already declining, the significant decrease in NAFLD listings was surprising. Other investigators have speculated that older patients and those with diabetes and obesity may have been more hesitant to seek medical care during COVID due to their known increased risk of adverse outcomes.(7)

This new and highly provocative data indisputably shows that ALD is now the leading indication for liver transplant (LT) accounting for 40% of all newly listed patients. However, pandemic-era drinking may not be the only cause of increased ALD listings and transplants. The rate of ALD listing rose as early as July 2020, which would likely not allow enough time for the impact COVID-era alcohol use. However, given inherent limitations of the UNOS data set, granular data on the amount and recency of alcohol use was not available. We also cannot discern from UNOS data if overall rates of decompensated ALD and severe AH increased in the COVID era in the general US population. However, there are suggestions from other single and multi-center studies that rates of AH may have risen during COVID.(8) In addition, the authors show that the rate of high MELD ALD listings and transplantations rose in states with longer stay-at-home orders, suggesting a causal link between longer stays at home, increased alcohol consumption, and subsequent listing for LT.

Other factors may also have impacted the evolving etiologies of liver failure amongst LT patients (**Figure 1**). First, the rise in ALD listing may, in part, be due to increased leniency for historic rules about the duration of pre-LT abstinence and pre-LT SUD treatment (i.e. “6-month rule”).(9) Prior to COVID, there were increasing reports of favorable 1-year outcomes in carefully selected patients with severe AH that were comparable to non-ALD patients. During the pandemic, it is possible that transplant centers were evaluating larger numbers of younger, previously healthy ALD patients with high MELD scores, which may have led to a recalibration of listing criteria. In fact, this study notes that ALD patients were significantly younger and sicker during the pandemic compared to the prior 5 years; this likely reflects a shift in listing practices and attitudes towards acute alcohol consumption precipitating more severe ALD. Second, in February 2021 UNOS implemented a new liver allocation policy designed to reduce geographic disparities, allowing for increased sharing of organs to high MELD transplant candidates across greater distances and reduced priority for patients listed with exception points. This policy change coincided almost exactly with the onset of the COVID pandemic, making its influence challenging to disentangle. An early analysis of the impact of this policy change found a surprising *increase* in between-center variation in median MELD at transplantation as well as an *increase* in distance traveled

for procurement, which may simply reflect evolving procurement practices that were confounded and exacerbated by a change in the waitlist pool.(10) Nonetheless, there is likely a direct relationship between increased alcohol use in the COVID-era and the number of patients listed for LT with ALD.

The increase in transplantation for ALD will likely continue as COVID-era drinking results in more patients hospitalized with the sequelae of excessive alcohol use. Of concern from a resource allocation perspective is that the number of patients with severe ALD alone could outstrip the entire national supply of donor organs. In addition, the prognostic utility of the MELD-Na score is increasingly recognized as being less reliable in ALD patients with high MELD scores that actually have a mortality rate comparable to non-ALD patients with lower MELD scores.(11) With that in mind, several groups have suggested that a minimum duration of abstinence for patients with ALD and particularly concomitant acute kidney injury may be reasonable to facilitate hepatic recovery and avoid unnecessary transplants. However, this does not imply that patients with ALD are less deserving of LT.

All of these factors create a complicated discussion about equity and justice in modern LT practice. There is an urgent unmet need for prospective, registry studies to answer the following questions about patients undergoing LT for severe AH or acute on chronic alcoholic cirrhosis without a window for sobriety or pre-LT rehabilitation:

- What objective medical, psychiatric, and psychosocial criteria should be used to minimize disease recurrence and lead to favorable long-term outcomes (i.e. MILAN-like criteria for ALD)?
- What are the intermediate and long-term outcomes in patients with severe AH?
- Has the shift towards candidates with ALD inadvertently or disproportionately impacted the wait-list mortality of other patient groups (i.e. NAFLD, HCC patients, HCV)?
- What is the impact of insurance type (private versus public) and other sociodemographic factors on ALD candidacy for LT?

Individual transplant centers also need to carefully reflect on these issues and ensure they are providing optimal clinical care to all of their patients with ALD:

- Is there a multi-disciplinary team including social workers and SUD experts available to assess and treat co-morbid psychiatric and behavioral disorders for both inpatient and outpatient evaluations ?
- Should all patients with severe AH have failed a course of steroids (or have a contraindication) prior to waitlisting?

- Should anti-craving and other psychoactive drugs be used in hospitalized AH patients before and after transplant?
- What immediate, intermediate, and long-term monitoring should ALD transplant patients undergo (e.g. serum pETH, other alcohol biomarkers, telemedicine visits)?
- What is the optimal immunosuppressive protocol for severe AH patients? Are they more prone to hospital-acquired and opportunistic infections?
- What is the incidence of post-LT recurrent alcohol use? Are there validated risk factors? What type of medical, psychiatric, and psychosocial interventions are most effective for prevention and/or treatment of recurrent AUD?

Outside of research and individual center reflection, society at large must also examine these trends and consider system-wide changes to reduce the morbidity and mortality related to excessive alcohol use. Other countries have succeeded with public health measures that reduce access, reduce appeal to young people, and increase the cost of alcohol.(9) An alcohol tax has also been proposed as a solution to reduce ALD mortality. Finally, as members of the hepatology community, we must advocate locally and nationally for resources that could turn the tide on this growing public health crisis, which has only accelerated in the fumes of the COVID pandemic.

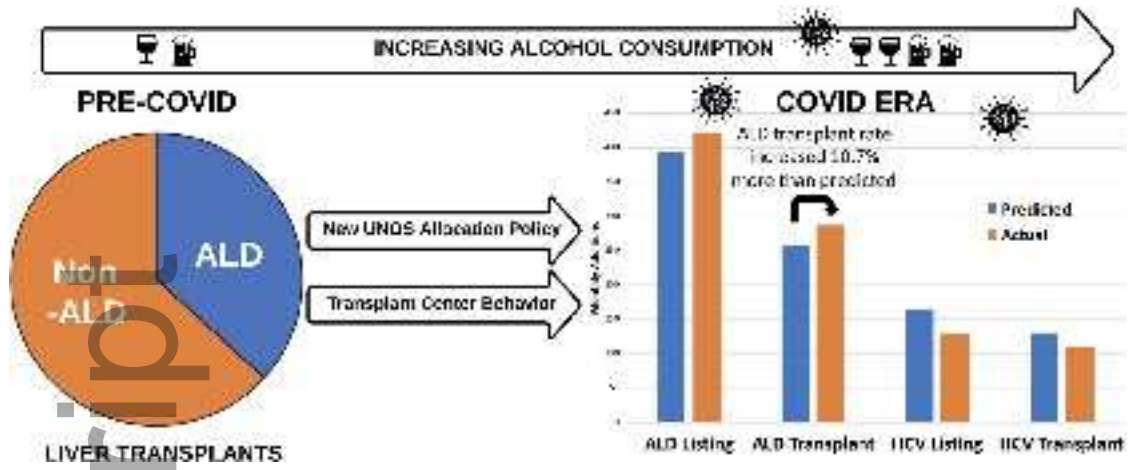
Figure legends

Figure 1 – Potential factors leading to an increase in waitlistings and liver transplantation for ALD in the pre-COVID (1/16-3/20) and post-COVID eras (4/20-12/20)

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