Alcohol-Associated Liver Disease Before and After COVID-19—An Overview and Call for Ongoing Investigation

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The Coronavirus Disease 2019 (COVID-19) pandemic has exacted a heavy toll on patients with alcohol-associated liver disease (ALD) and alcohol use disorder (AUD). The collective burden of ALD and AUD was large and growing, even before the COVID-19 pandemic. There is accumulating evidence that this pandemic has had a large direct effect on these patients and is likely to produce indirect effects through delays in care, psychological strain, and increased alcohol use. Now a year into the pandemic, it is important that clinicians fully understand the effects of the COVID-19 pandemic on patients with ALD and AUD. To fill existing gaps in knowledge, the scientific community must set research priorities for patients with ALD regarding their risk of COVID-19, prevention/treatment of COVID-19, changes in alcohol use during the pandemic, best use of AUD treatments in the COVID-19 era, and downstream effects of this pandemic on ALD. *Conclusion:* The COVID-19 pandemic has already inflicted disproportionate harms on patients with ALD, and ongoing, focused research efforts will be critical to better understand the direct and collateral effects of this pandemic on ALD. (*Hepatology Communications* 2021;5:1616-1621).

Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection, has had important direct and indirect effects on patients with alcohol-associated liver disease (ALD). Before the COVID-19 pandemic, the global toll of ALD was sizable, and COVID-19 has inflicted disproportionate negative effects on this population. Early data suggest that patients with chronic liver disease, and particularly those with ALD, may be at greater risk of mortality if infected by SARS-CoV-2.[1-3] Furthermore, the COVID-19 pandemic and resulting social and economic stressors have contributed to increased psychological strain for many individuals, including those with alcohol use disorder (AUD) and ALD. As a result, the pandemic is likely to enact collateral damage on this population through delays in care and increases in alcohol use. Changes in alcohol use patterns may lead to alcohol-associated hepatitis and liver-related mortality. At the current time, approximately 1 year since SARS-CoV-2 virus was first identified,[4] it is important that we assess the effects of this pandemic on patients with ALD and define research priorities needed to mitigate these effects.

Pre-COVID-19 ALD Burden

In the pre-COVID-19 era, the burden of AUD and ALD was large and growing. National data from the United States show that the prevalence of AUD and high-risk drinking has increased in recent years.[5]

Abbreviations: AAPC, average annual percentage change; ALD, alcohol-associated liver disease; AUD, alcohol use disorder; COVID-19, Coronavirus Disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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The diagnosis of alcohol-associated cirrhosis is on the rise,[6] and there have been corresponding increases in liver transplantation from ALD and alcohol-associated hepatitis.[7,8] There have also been larger numbers of ALD-related hospitalizations,[9] and inpatient costs attributable to ALD now total more than every other liver disease etiology combined.[10,11]

Based on national death certificate data, mortality from ALD is also on the rise.[12] Of concern, the average annual percentage changes (AAPC) in mortality rates have been most pronounced among younger individuals and women. The AAPC in mortality in women age 25-34 years was 6.07 (95% confidence interval [CI] 2.95-9.28) compared to women age 65-74 years with AAPC 1.81 (95% CI 0.92-2.71).

Alcohol cessation can arrest or even reverse ALD,[13] and AUD treatment is associated with lower decompensation rates, readmission, and mortality in patients with alcohol-associated cirrhosis.[14-16] Before COVID-19, implementation of AUD counseling or pharmacotherapy was only used among 10%-14% of patients with alcohol-associated cirrhosis.[5,14,15] Furthermore, there are concerning sex-based disparities with lower use of AUD treatment in women. This may be due to attitudinal barriers, more perceived stigma, and conflicting family or child-care responsibilities.[14]

Outcomes of Patients With ALD With COVID-19

There are many reasons why alcohol use and ALD may predispose to worse outcomes from COVID-19. First, alcohol use and associated liver disease disrupts the innate and adaptive immune systems by affecting the survival and function of immune cells important in mounting a defense against viral infections.[17,18] Second, chronic alcohol consumption is associated with an increased susceptibility to acute respiratory distress syndrome.[19-21] This may be related to alcohol's direct effects on immune function in addition to alveolar epithelial dysfunction and decreased concentration of pulmonary antioxidants in individuals with chronic alcohol abuse.[22] Third, patients with AUD often have other comorbidities, including metabolic syndrome, chronic kidney disease and tobacco use, which have been independently associated with severe COVID-19 outcomes.[23-25]

Although patients with cirrhosis do not appear to be at increased risk for SARS-CoV-2 acquisition,[26] there is now some direct evidence that among patients with liver disease, those with ALD fare worse with COVID-19. Data from an international registry study that included 179 patients (24%) with ALD demonstrated that cirrhosis, and particularly decompensated cirrhosis, was associated with worse outcomes from COVID-19.[1] Furthermore, even adjusting for potential confounders including medical comorbidities, ALD etiology was associated with an increased risk of mortality in COVID-19. Similar findings were reported in a U.S. multicenter study in which decompensated cirrhosis, hepatocellular carcinoma, and ALD were independent risk factors for mortality in patients with COVID-19.[2]

Changes in Alcohol Consumption Related to COVID-19

Effects of the COVID-19 pandemic unrelated to SARS-CoV-2 infection itself may prove to have the

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biggest effect on patients with ALD. Undoubtedly, COVID-19 will enact massive collateral damage through the effects of deferred care, medication nonadherence, increased consumption of food, and more high-risk alcohol use.[27,28] The pathophysiology of ALD is complex but overall alcohol dose and pattern of consumption are both strongly implicated in the risk of ALD.[29] Increased alcohol consumption during the COVID-19 pandemic therefore has the potential to lead to increased morbidity and mortality.

A number of COVID-19-related factors have the potential to increase alcohol use in patients with AUD or excess drinking. Factors that increase alcohol use may include adverse economic effects resulting from the COVID-19 pandemic, disruptions in work and education, psychosocial stressors associated with limitations on social gatherings, social isolation with decreased or lack of social support system, and shifts in alcohol consumption from bars/restaurants to at-home use.[30]

Epidemiologic and marketing data during the early days in the pandemic showed a spike in alcohol use in the general population. In April 2020, online sales of alcohol in the United States were up 477%, and brick-and-mortar sales were up 26% compared with sales from the previous year.[31] Postpandemic increases in alcohol purchases were most pronounced in younger adults, households with children younger than 18 years, and ethnic minorities.[32] Similar findings were demonstrated in Canada, where there was a 38% relative increase in monthly alcohol sales in March 2020 compared with March 2019.[33] Online sales may have lower cost per unit of alcohol, which could lead to increased consumption. Additionally, sales of larger packs of alcohol including boxes of wine, large-volume (e.g., 1.75 L) liquor bottles, and 30-packs of beer have all increased compared with previous years.[31] Emerging data suggest that individuals, and particularly females, are engaging in an increased frequency of alcohol consumption and binge drinking.[34,35] In sum, these data imply that increasing trends in alcohol sales are translating to increased alcohol consumption and are not attributable to increased alcohol stockpiling alone.

Some concerning trends have also been shown in individuals with AUD. Researchers in the United Kingdom identified individuals with pre-existing alcohol disorders and performed a cross-sectional telephone survey 2 months after their national lockdown.[36] Of the 182 participants, 24% reported an increase in their alcohol use, consuming an average of 48.8 units of alcohol (approximately 5.5 bottles of wine, 1.5 bottles of spirits, or 16 pints of beer) per week after lockdown. In contrast, only 19% reported a decrease in alcohol intake.

There are already some early signs that accelerations in alcohol-associated health effects among women may worsen in the COVID-19 era. During the pandemic, women have taken on a disproportionate amount of work at home and have borne a higher economic burden than men.[37] There are some early data suggesting that this may be leading to larger increases in alcohol use and alcohol-associated health effects in women.[38] As mentioned previously, there is lower use of AUD treatment among women.[14] It is unclear how this may change in the COVID-19 era, given expanded options for AUD treatment, including virtual counseling and online Alcoholics Anonymous meetings.

Downstream Effects of COVID-19 on Patients With ALD

Given the association between alcohol use and poor outcomes in ALD, COVID-19-related changes in alcohol consumption have the potential to lead to direct alcohol-associated health effects, including alcohol-associated hepatitis and liver-related mortality. Furthermore, depending on program requirements for pretransplant abstinence, alcohol relapses could lead to decreased transplant referrals and wait-list drop-off in pre–liver-transplant patients. Although it is still too early to fully assess the effect of changes in alcohol consumption patterns in the wake of the COVID-19 pandemic, there are some early data that are concerning.

In the spring of 2020, as the U.S. COVID-19 outbreak was beginning, there were some signs that patients with cirrhosis were delaying care. Data from the National Veterans Affairs health care system show a rapid drop-off in cirrhosis admissions beginning in March of 2020 compared with historic data from the previous year.[39] Patients admitted later had higher Model for End-Stage Liver Disease scores, suggesting that only the sickest patients were coming in for care. In addition, there was a very

slight increase in the proportion of cirrhosis-related hospitalizations among patients with ALD compared to other etiologies.

Increases in alcohol consumption in the COVID-19 era also have the potential to contribute directly to the burden of ALD. Some have raised concern that increased harmful drinking in the wake of COVID-19 could contribute to an increasing incidence of alcohol-associated hepatitis.[30] Early anecdotal reports that alcohol-associated hospitalizations have increased[40] are now corroborated by a single-center study demonstrating an increasing number of hospitalizations and liver transplants among patients with ALD in the COVID-19 era.[41]

Changes in alcohol consumption in the COVID-19 era could also have huge implications on patients listed for transplantation. In the previously mentioned telephone survey conducted in the United Kingdom,[36] 17% of patients who were abstinent before the lockdown experienced a relapse during lockdown. If similar patterns of alcohol relapse are occurring in patients listed for transplant, this could negatively impact the listing status of many patients.

Call for Ongoing Investigation of COVID-19 and ALD

To mitigate the downstream effects of the COVID-19 pandemic on patients with ALD, there is an urgent unmet need to identify, investigate, and address clinically important questions relevant to this population (Table 1). These research priorities should fit within the larger framework of ongoing strategies to address the growing burden of ALD and AUD.[42] Specific areas that deserve further attention include COVID-19 outcomes in ALD, with and without cirrhosis; COVID-19 treatments for patients with chronic liver disease and ALD; safety and efficacy of the COVID-19 vaccine in patients with ALD; the effects of the COVID-19 pandemic on alcohol use patterns; the efficacy of remote AUD counseling such as digital or virtual technology and use of telemedicine; and changes in the incidence of alcohol-associated health effects including alcohol-associated hepatitis, alcohol-associated acute-on-chronic liver failure, alcohol-associated cirrhosis, and decompensations in patients with established cirrhosis. Furthermore, additional discussion of transplant-listing policies for patients who relapse during the pandemic is critical, given the unique and challenging stressors related to the COVID-19 pandemic.

Such research efforts have the potential to inform the clinical care of patients with ALD, including tailored COVID-19 treatment guidelines and guidance on the optimal use of corticosteroids in patients with severe alcohol-associated hepatitis infected with SARS-CoV-2. This work could also have immediate policy implications including informing vaccination strategies and recommendations regarding shielding (i.e., minimizing all face-to-face contact for extremely clinically vulnerable) for patients with ALD and better understanding factors that may contribute to increased alcohol use. Additionally, these efforts could explore potential disparities in alcohol consumption and ALD by sex and race/ethnicity, determine care delivery models best suited to address AUD, and inform transplant listing decisions for patients who experience relapse during the COVID-19 pandemic.

The National Institutes of Health and National Institute on Alcohol Abuse and Alcoholism have prioritized investigation of alcohol use in the era of COVID-19. There are new Requests for Applications for grants that address the relationship between alcohol consumption and outcomes of COVID-19, including the impact of alcohol misuse on COVID-19 incidence and severity and effects of pandemic-related restrictions on high-risk drinking and AUD.[43]

Conclusions

Before COVID-19, alcohol-associated liver disease had a massive and growing burden. Early in the COVID-19 pandemic, we observed worse outcomes from COVID-19 infections among patients with ALD. There has also been significant collateral damage related to the pandemic, including psychosocial strain and limited access to health care, which may lead to more high-risk drinking. Increases in the frequency and amount of alcohol intake have the potential to increase morbidity and mortality in patients with ALD. There are already some early signs that patients

TABLE 1. RESEARCH PRIORITIES FOR COVID-19 AND ALD

Research Priority	Clinical/Policy Implications
Risk and Outcomes of COVID-19 in ALD	
Incidence of COVID-19 infection in ALD	• Inform recommendations regarding shielding (i.e., avoidance of all person-to-person contact in extremely vulnerable) for patients with ALD
COVID-19 outcomes in patients with ALD	• Better understanding of relative influences of alcohol use and underlying liver disease on COVID-19 outcomes • Tailored clinical care guidelines for patients with ALD
Treatment of alcohol-associated hepatitis and COVID-19	• Determine the optimal use of corticosteroids in patients with alcohol-associated hepatitis and COVID-19
COVID-19 Therapies/Vaccination	
Efficacy of COVID-19 therapies in ALD	• Provide clinical guidance for SARS-CoV-2 infections in patients with ALD
Risks of COVID-19 therapies in ALD	• Provide clinical guidance for SARS-CoV-2 infections in patients with ALD • Better inform patients on expected risks of these therapies
Safety and efficacy of COVID-19 vaccinations in ALD	• Magnitude/duration of vaccine response • Effect of liver disease severity on vaccine response • Need for additional booster doses for adequate immunologic response and protection • Risk of liver injury
Alcohol Use During COVID-19 Pandemic	
Patterns of alcohol consumption during the COVID-19 pandemic	• Determine whether increased online sales of alcohol translate into increases in overall consumption • Inform policy that could reduce harms from alcohol use during the pandemic
Factors associated with unhealthy alcohol use during COVID-19	• Ascertain policy priorities (e.g., alcohol pricing, depression/anxiety treatment, unemployment benefits) to address AUD during COVID-19
Disparities in alcohol consumption by sex and race/ethnicity	• Identify high-risk populations who may benefit from targeted interventions • Assess effects of concurrent non-COVID-19-related stressors, including social unrest, because of racial disparities and polarizing politics
AUD Treatments During COVID-19 Pandemic	
Efficacy of remote alcohol use counseling and monitoring	• Inform reimbursement policy in the post-COVID-19 era • Assess benefits of continuing remote alcohol-use treatment for select patients • Determine care delivery models (e.g., telemedicine, video counseling) that are best suited for AUD
Downstream Effects of COVID-19 on ALD	
Incidence of alcohol-associated hepatitis, alcohol-associated acute-on-chronic liver failure and cirrhosis	• Address disparities by sex and race/ethnicity • Better account for hepatology care needs in the post-COVID-19 era • Expansion in AUD counseling resources
Transplant considerations for patients with ALD who relapsed	• Inform transplant-listing policy decisions for patients who experience relapse during COVID-19 pandemic

with ALD are experiencing poor outcomes in the wake of COVID-19, including delays in care and an increase in alcohol-associated hepatitis. Furthermore, an increase in relapses or an inability to confirm sobriety in the COVID-19 era has the potential to lead to transplant-listing challenges for many patients. Ongoing investigation is critical to better understand the collateral damage on patients with ALD.

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