Epidemiology and Disease Burden of Alcohol Associated Liver Disease

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Consumption of alcohol in excess leads to substantial medical, economic, and societal burdens. Approximately 5.3% of all global deaths may be attributed to alcohol consumption. Moreover, the burden of alcohol associated liver disease (ALD) accounts for 5.1% of all disease and injury worldwide. Alcohol use disorder (AUD) affects men more than women globally with significant years of life loss to disability in low, middle and well-developed countries. Precise data on global estimates of alcohol related steatosis, alcohol related hepatitis, and alcohol related cirrhosis have been challenging to obtain. In the United States (US), alcohol related steatosis has been estimated at 4.3% based on NHANES data which has remained stable over 14 years. However, alcohol-related fibrotic liver disease has increased over the same period. In those with AUD, the prevalence of alcohol related hepatitis has been estimated at 10–35%. Globally, the prevalence of alcohol-associated cirrhosis has been estimated at 23.6 million individuals for compensated cirrhosis and 2.46 million for those with decompensated cirrhosis. The contribution of ALD to global mortality and disease burden of liver related deaths is substantial. In 2016 liver disease related to AUD contributed to 50% of the estimated liver disease deaths for age groups 15 years and above. Data from the US report high cost burdens associated with those admitted with alcohol-related liver complications. Finally, the recent COVID-19 pandemic has been associated with marked increase in alcohol consumption worldwide and will likely increase the burden of ALD. (J Clin Exp Hepatol 2023;13:88–102)

The consumption of alcohol has been prevalent in different cultures for many centuries. Based on a recent analysis in 2014, the cultural influence has remained an essential correlate of alcohol use and misuse for over 75 years.[1] Consumption of alcohol in large quantities can lead to substantial medical, economic, and social burdens on societies in terms of morbidity and mortality. According to reports from WHO in 2016, about 5.3% of all global deaths were attributed to alcohol consumption or approximately 3 million deaths on a global scale.[2] The global burden of alcohol-associated liver disease accounts for about 5.1% of disease and injury worldwide, is one of the most frequent causes of death in the world, ranking 30th, and is directly related to the amount of alcohol consumption.[3] Globally, AUD affects men more than women and is the second most disabling disease and injury condition for men.[4] One estimate suggests that AUD may cause 18.4 million years of life lost to disability (YLD) which extrapolates to about 3.5 percent of all YLDs, in low and middle-income countries and 5.7 percent of all YLDs in well-developed countries.[4,5] In this review, we will discuss the evolving nomenclature and standard measurements for AUD, as well providing estimates for disease burden across the spectrum of alcohol-associated liver disease and factors that contribute to progression of alcohol-associated liver disease. Finally, we will address the effects of the recent COVID-19 pandemic on the disease burden of ALD.

DEFINITIONS ASSOCIATED WITH AUD

When estimating the epidemiological burden of alcohol associated liver disease, it is important to understand the different definitions used in association with AUD. Binge drinking, heavy drinking, or any drinking by pregnant women or people younger than 21 is considered excessive drinking. According to NIAAA (National Institute of Alcohol Abuse and Alcoholism) guidelines, binge drinking includes four or more drinks for women and five or more

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Abbreviations: AAPC: Average annual percentage change; ABIC: Age, Serum bilirubin, INR and serum Creatinine; ABV: Alcohol by volume; ALD: Alcohol-associated liver disease; AUD: Alcohol use disorder; BAC: Blood alcohol concentration; CDC: Centers for Disease Control and Prevention; COVID-19: Coronavirus disease 2019; GAHS: Glasgow alcoholic hepatitis score; HE: Hepatic encephalopathy; HRS: Hepatorenal syndrome; ICD-10: International Classification of Diseases, 10th Edition; MDF: Maddrey's Discriminant Function; MELD: Model of end-stage liver disease; MRI: Magnetic resonance imaging; NIAAA: National Institute of Alcohol Abuse and Alcoholism; NIS: National inpatient sample; NHANES: National Health and Nutrition Examination Survey; NSDUH: Annual National Survey on Drug Use and Health; SAMHSA: Substance Abuse and Mental Health Services Administration; US: United States; USG: Ultrasonography; WHO: World Health Organization; YLD: Years of life lost to disability
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drinks for men on a single occasion or in 2 h. This equates to a drinking pattern that can increase blood alcohol concentration (BAC) to 0.08 percent or 0.08 g of alcohol per deciliter or higher.[6] In contrast, *heavy drinking* is defined as the consumption of more than three drinks on any day or more than seven drinks per week for women and four drinks on any day or more than fourteen drinks per week for men[4] Other classifications include the Annual National Survey on Drug Use and Health (NSDUH), conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA), which defines *binge drinking* as five or more alcoholic drinks for males or four or more alcoholic drinks for females on the same occasion (i.e., at the same time or within a couple of hours of each other) on at least one day in the past month. Though immoderate drinking does not necessarily make a person alcohol dependent, the risk of AUD increases significantly with binge drinking and heavy alcohol use.[7]

The Centers for Disease Control (CDC) has provided guidance for the amount alcohol in a standard drink with a standard drink comprising 12 ounces of 5% alcohol by volume (ABV) for beer, 8 ounces of 7% ABV for malt liquor, 5 ounces of 12% ABV for wine, and 1.5 ounces of 40% ABV distilled spirits or alcohol, including gin, rum, vodka, and whiskey. In addition, the CDC estimates that excessive drinking is responsible for approximately 88,000 deaths per year, with a total economic cost burden of 249 billion per year that excludes costs from motor vehicle accidents, violence, injuries, risky sexual behaviors, and chronic conditions such as cancer, hypertension, and heart diseases.[8]

As we discuss the disease burden of ALD, it is important to note that more than 30 conditions are associated with alcohol consumption, with alcohol being the primary driver in these cases according to WHO *International Classification of Diseases, 10th Edition* (ICD–10).[9] AUD remains one of the most critical disease illnesses in this group and entails alcohol dependence and alcohol abuse. AUD is associated with considerable disability, being the fourth most disabling disease category in low to middle-income countries and the third most disabling disease category in well-developed countries according to a recent report.[10] Based on reports from 2016 National Survey on Drug Use and Health, approximately 136 million US citizens aged 18 and older drink alcohol, with 65.3 million reporting binge drinking in the past month, accounting for half (47%) of the current alcohol users. In addition, 16.3 million also reported heavy drinking in the past month and accounting for 24.9% of individuals who reported binge drinking and 11.9% of individuals with current alcohol use.[11] Approximately 35,000 deaths per year are attributable to alcohol-associated cirrhosis, making alcohol-associated liver disease (ALD) one of the two leading indications for liver transplant.[11,12]

KEY POINTS

Different definitions used in association with AUD are important in order to understand the epidemiological burden of alcohol associated liver disease. Approximately, 35,000 deaths per year are attributable to alcohol associated cirrhosis, making ALD as one of the two leading indications for liver transplant.

The Spectrum of Alcohol-associated Liver Diseases

In the Western world, AUD represents one of the most common causes of liver damage. The spectrum of liver diseases associated with AUD ranges from simple steatosis, to steatohepatitis, fibrosis, cirrhosis, and cancer.[13] The International Classification of Diseases (ICD-10) recognizes these stages of liver damage, including steatosis, steatohepatitis, and early fibrosis, as being considered reversible, while late stages constituting cirrhosis and liver failure and cancer are considered severe and irreversible (Figure 1).[14] The various stages of ALD and severity are directly related to the amount of alcohol consumed.[15] Literature suggests that alcohol consumption of more than 80 g/day in men and 20 g/day in women is associated with liver cirrhosis.[16] A study from northern Italy examined a total of 6534 subjects, indicating an increased risk of developing either noncirrhotic alcohol-induced liver injury or alcohol-associated cirrhosis in both men and women who consumed at least 30 g of alcohol per day and the risk of ALD substantially increased with increasing alcohol intake.[17]

Fatty liver (steatosis) is the earliest, most common response of the liver to moderate or large doses (i.e., binge drinking) of alcohol and chronic ethanol consumption. This is attributed to changes in lipid metabolism in the liver with an increase in lipid synthesis and decreased lipid metabolism, causing lipid storage in the hepatocytes. Though fatty liver caused by alcohol consumption was once considered benign, it is now recognized as the leading risk factor for liver disease progression and even cirrhosis.[18] Dose and duration of alcohol intake remain the primary drivers of alcohol-related steatosis in this case though the exact amount of alcohol intake required for the development of steatosis remains controversial. Based on a study done by Lieber *et al.*, hepatic steatosis may develop after 2–3 weeks of excessive alcohol intake (120–150 g/dl per day), and if alcohol consumption continues, there may be progression to severe inflammation with alcohol-related hepatitis.[19,20]

Alcohol-related hepatitis has been associated with high rates of mortality and morbidity, with severe cases having

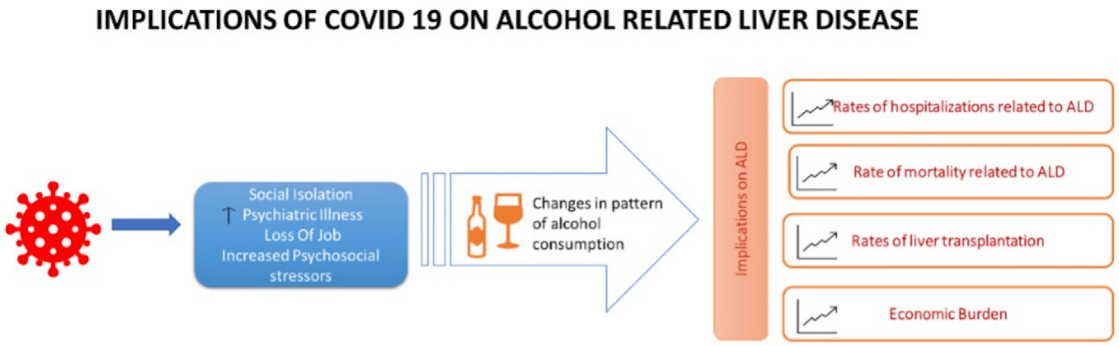

Figure 1 Implications of COVID 19 on alcohol related liver disease.

short term (30 day) mortality rates ranging between 30 and 50 percent.[21,22] Alcohol-related hepatitis is characterized by a constellation of clinical signs and symptoms including fever, elevated bilirubin levels (>2), coagulopathy, and liver-related complications such as ascites, volume overload, hepatic encephalopathy, and GI bleeding. Several prognostic scores have been used to predict short-term mortality in these patients. These include MDF (Maddrey's Discriminant Function), MELD (Model of End-stage Liver Disease), ABIC (Age, Serum bilirubin, INR and serum Creatinine), GAHS (Glasgow Alcoholic Hepatitis Score), and Lillie model. The role of these scoring systems remains limited to determining the long term survival of these patients, as they depend primarily on abstinence from alcohol.[22]

Excessive and continued alcohol consumption increases the risk of developing alcohol-related cirrhosis.[23] The exact amount of alcohol consumption for the development of alcohol-related hepatitis and its progression to liver cirrhosis is not yet determined. However, based on prior observational studies, ingestion of more than >20 g of alcohol per day in women and >80 g per day in men is associated with an increased prevalence of liver cirrhosis.[17] Signs and symptoms of patients with alcohol-related cirrhosis are similar to other chronic liver diseases and can be further characterized into compensated and decompensated liver cirrhosis. Decompensated liver cirrhosis is associated with complications such as ascites, hepatic encephalopathy (HE), GI bleeding, hepatorenal syndrome (HRS), and death.[14]

KEY POINTS

Various stages and severity of ALD is directly related to amount of alcohol consumed. The International Classification of Diseases (ICD-10) recognizes these stages of liver damage, including steatosis, steatohepatitis, and early fibrosis, as being considered reversible, while late stages constituting cirrhosis and liver failure and cancer are considered severe and irreversible.

Incidence and Prevalence of Alcohol Related Steatosis, Alcohol Related Hepatitis, and Alcohol-Related Cirrhosis

Epidemiology of Alcohol-related Steatosis

The prevalence of alcohol related steatosis is challenging to ascertain in the general population as many patients do not seek medical attention due to the asymptomatic nature of the disease.[24] The estimated prevalence also depends on the diagnostic modality used to screen for steatosis. Methods used to ascertain steatosis include ultrasonography (USG), magnetic resonance imaging (MRI), and liver biopsy. Amongst these, USG is the least expensive and non -invasive method with a sensitivity of 60–90 percent and specificity of 90–95 percent, making it an acceptable choice in the clinical care setting. Magnetic resonance imaging increases the accuracy of detection of alcohol-related steatosis and can help quantify the degree of hepatic steatosis though it is an expensive modality.[25] Liver biopsy remains the gold standard for detection of steatosis; however, its routine use is limited by its invasive nature and related complications, making it a less desirable choice and impractical modality in the clinical setting for steatosis assessment.[26]

The prevalence of alcohol-related steatosis in the US has been estimated using NHANES data derived from questionnaires, abdominal ultrasonography, and laboratory tests. Based on one study, the prevalence of alcohol related-steatosis was around 4.3 percent in the US population among 34, 423 respondents. There was a stable trend over the last 14 year study period from 2001 to 2016; however alcohol-related steatosis associated with stage 2 fibrosis showed an increasing trend from 0.6 to 1.5 percent.[27,28] Though alcohol-related steatosis has been considered a benign condition, it is now known that there may be progression to advanced fibrosis and cirrhosis, leading to increased morbidity and mortality rates in this patient population. A recent meta-analysis estimated the annual rate of progression of alcohol-related steatosis to cirrhosis at approximately 3 percent, with mortality rate of 6 percent. Interestingly, these patients who progress also tend to have increased mortality from non-hepatic causes when compared with liver-specific mortality rates.[29]

Table 1 Estimated Prevalence of Alcoholic Liver Disease (ALD) in US Using NHANES Data Comparing Years 2001–2002 and 2015-2016.[29]

Alcoholic Liver Disease (ALD)	Year: 2001–2002	Year: 2015–2016
Overall weighted Prevalence of ALD	8.8% (95% CI: 7.6–9.9)	8.1% (95% CI: 6.5–9.6)
ALD with Stage ≥3 Fibrosis	2.2% (95% CI: 0.4–4.0)	6.6% (95% CI: 2.0–9.9)
Prevalence of ALD in Men	9.7% (95% CI: 7.9–11.4)	9.0% (95% CI: 6.2–11.7)
Prevalence of ALD in Women	8.0% (95% CI: 6.3–9.7)	7.2% (95% CI: 5.9–8.5)
Prevalence of ALD with Stage ≥3 Fibrosis in Men	2.4% (95% CI: 0.01–9.0)	7.3% (95% CI: 0.01–15.5)
Prevalence of ALD with Stage ≥3 fibrosis in Women	2.6% (95% CI: 0.4–4.8)	4.6% (95% CI: 0.01–9.2)

Abbreviation: ALD, Alcohol-associated liver disease.

Another retrospective study using NHANES data analyzed and compared the prevalence of ALD also over the period of 2001–2016. In this study the overall weighted prevalence of ALD remained stable at 8.8% (95% CI: 7.6–9.9) and 8% (95% CI: 6.5–9.6) in the year 2001–2002 and 2015–2016 respectively (P = 0.102). However, there was an increase in the prevalence of Stage 3 fibrosis in ALD patients from 2.2% (95% CI: 0.4–4.0) to 6.6% (95% CI: 2.0–9.9) over the same period (P = 0.007). Based on the same survey study, the estimated national prevalence of ALD and ALD with stage 3 fibrosis was calculated to be 17.8 million (95% CI: 14.3–21.3) and 1.1 million (95% CI: 0.4–1.8) in the year 2015–2016. The sex specific trends remained stable over the study period, though there was higher prevalence of ALD in men compared to women.[27] (Table 1).

KEY POINTS

Based on NHANES data from 2001 to 2016, alcohol related steatosis has been stable over the last 14 year study period, while stage 2 fibrosis associated with alcohol related steatosis showed an increasing trend from 0.6 to 1.5 percent.

Epidemiology of Alcohol-related Hepatitis

The precise incidence and prevalence of alcohol-related hepatitis are not known with one of the main challenges being asymptomatic patients often remain undiagnosed. According to a study conducted by Naveau *et al.*, the prevalence of alcohol related hepatitis was approximately 20% in a cohort of 1604 patients with AUD with available liver biopsies. Approximately 10–35% of individuals with AUD will have changes consistent with alcohol related hepatitis and an estimate of the prevalence of alcohol-related hepatitis can be extrapolated based on the prevalence of AUD. In the US, the prevalence of AUD has been estimated at 16 million people, or 8% of the general population; hence the number of individuals with AH in the US may approximate up to 5 million individuals.[30]

The National Inpatient Sample (NIS) Database also provides insights into the epidemiology of AH in the US. Based on inpatient data an increase in AH-related hospitalizations has been reported from 2002 (249,884 or 0.66% of total admission in 2002) to 2010 (326,403 or 0.83% of total admissions). There was also an increased rate of readmissions in this patient population given the significant co-morbidities and complications including increased rates of sepsis, acute renal insufficiency, and gastrointestinal bleeding[31] (Table 2). Reported readmission rates in these patients range from 20 to 25% at 30 days to 37% at 90 days after discharge. Based on data from National Readmission Database involving 21,572 individuals with alcohol-related hepatitis, the annual cost burden at 30 day and 90 day for AH-related readmissions was approximated at $164 million for 30 day readmissions and $321 million for 90 day readmissions respectively in this cohort.[32] In addition, rates of rehospitalizations based on an analysis of over 15,000 commercially insured adults with AH demonstrated more than 50% of survivors were hospitalized within one year and 75% through the second year with total number of readmissions reaching as high as 40,000. The total health care costs were approximated at $2.2 billion over a 5 year period including costs of care associated with liver transplantation.[33] Based on a recent systematic review of 7528 participants, the annual rate of progression of AH to cirrhosis was estimated at 10% with a similar rate of progression to cirrhosis of 8% noted in those with fibrotic liver disease. In addition, there is a significant increase in mortality in patients with alcohol related hepatitis ranging from 5 to 15% annually with the highest rates noted in those with alcohol related hepatitis who required inpatient level of care[29] (see Table 3).

Table 2 Trends in Alcoholic Hepatitis Related Hospitalizations, Financial Burden and Mortality Rates in USA Using NIS Data Base Analysis (2002–2010).[33]

	2002	2003	2004	2005	2006	2007	2008	2009	2010
Alcohlic hepatitis related hospitalizations	249,884 (0.66)	249,437 (0.65)	265,072 (0.69)	265,174 (0.68)	286,160 (0.73)	286,018 (0.72)	301,197 (0.76)	310,745 (0.79)	326,403 (0.83)
Overall health care cost ($)	25,276 ± 390	30,049 ± 500	28,639 ± 400	32,077 ± 470	34,033 ± 446	36,601 ± 520	37,820 ± 514	39,998 ± 524	40,870 ± 488
Mortality (%)	8	8.1	7.5	7.5	7.1	6.5	5.9	5.6	5.1

Abbreviation: NIS, National inpatient sample.

KEY POINTS

Based on NIS data base analysis, there has been an increase in the rate of readmissions in patients with alcohol related hepatitis due to higher rates of complications such as sepsis, acute renal insufficiency, and gastrointestinal bleeding in this patient population. In addition, there is a significant increase in mortality in patients with alcohol related hepatitis ranging from 5 to 15% annually with the highest rates noted in those with alcohol related hepatitis who required inpatient level of care.

Epidemiology of Alcohol-associated Cirrhosis

According to a systematic analysis for the global burden of disease study in 2017, the global prevalence of ALD has been estimated to be around 23.6 million and 2.46 million for both compensated and decompensated cirrhosis respectively. There has been an increasing trend towards age-standardized prevalence of patients with decompensated cirrhosis from all etiologies that has occurred from 1990 to 2017 with prevalence increasing from 25.3 per 100,000 in 1990 to 30 per 100,000 in 2017. On the other hand, the trend for compensated cirrhosis has been relatively stable with 290 per 100,000 in 1990 to 288.1 per 100,000 in 2017.[34] Based on reports from NHANES survey from 1988 to 1994 and 1999–2016, the total prevalence of ALD has been relatively stable in the US from 1988 to 2016.[35] However, as noted previously, patients with advanced fibrosis in stages 3 and 4 increased significantly from 2.2 percent in 2002 to 6.6 percent in 2015 and 2016.[27] This has been reflected in an estimated increase in rates of hospitalization in patients with alcohol-associated cirrhosis with retrospective analyses in the US noting a 32.8 percent increase in liver cirrhosis related to AUD per 1000 patients with mortality rates as high as 8 percent.[27,29] Another observational study done in 2017 estimated the highest average annual percentage change (AAPC) in mortality from cirrhosis of any cause in patients aged 25–34 from year 2009–2016 was 10.5% with CI of 8.9%–12.2% around AAPC.[36] Thus, it is not surprising that an 63.4% increase in the listing of these patients for liver transplants was observed during this period.[27]

A recent study based on NIS database analysis from 2007 to 2014 evaluated annual trends of hospitalizations in patients with alcohol-associated cirrhosis and further stratified it based on age, race and sex yielding useful information about predictors of mortality in these patients. Among 159, 973 hospitalizations with ALD, 83.7% (133, 929) were identified as patients with alcohol-associated

Table 3 Preliminary Reports on Effect of COVID Pandemic on Drinking Patterns Worldwide.

Author	Population	N	Findings
Grossman *et al.*[47]	US adults above 21 yrs.	832	Increase in binge drinking and frequency of alcohol use
Chartier *et al.*[52]	US adults 18 yrs and older	5874	Increased frequency of alcohol use during 3rd wave of COVID-19 amongst users of multiple social media platforms
Zipursky *et al.*[53]	Canadian study	NA	Increase in alcohol sales and alcohol related emergencies
Sidor *et al.*[54]	Polish residents	1097	Increase in alcohol consumption was seen in 14.6%, with a higher tendency to drink more in individuals with AUD
Kar *et al.*[55]	Pregnant individuals in Canada	7470	6.7% of pregnant females reported increased alcohol use
Boschuetz *et al.*[56]	US adults	417	Increase in AUDIT C score in females, increase in the frequency and quantity of alcohol use as well as the frequency of alcohol use prior to 5 pm.
Hanson *et al.*[57]	American Indian women	62	Increase in drinking amongst binge drinkers by 24.2%, over half had at least one binge drinking episode. Approximately half reported reduced drinking.
Vandenberg *et al.*[60]	Australian residents >15 yrs old	N/A	Reduction in on premises beer per capita consumption during first wave restrictions of COVID pandemic while partial removal of restrictions resulted in immediate increase in on premise beer per capita consumption
Naughton *et al.*[61]	UK residents 18 yrs or older	1044	Increased alcohol intake (AUDIT C scores) during first wave of COVID pandemic
Bollen *et al.*[62]	French speaking Belgian adults	1693	Decreased their alcohol consumption after lockdown onset and returned to their initial alcohol consumption after lockdown offset
Hagit Bonny Noach[63]	Israeli adult residents age 18-65	750	Participants who experienced two lockdowns reported more frequent consumption of all alcoholic beverages and cannabis in the last 30 days than those who experienced one lockdown
Szajnoga *et al.*[65]	Polish adults	4072	Increased alcohol use amongst particular groups including men, 18–24 yrs of age, inhabitants of big cities, and remote workers
Sallie *et al.*[66]	Multinational adults 18yrs or older	2873	36% adults reported an increase in alcohol use during COVID-19 pandemic
Mangot Sala *et al.*[67]	Netherland	63,194	Decreased alcohol consumption during COVID pandemic compared to previous years
Bonar *et al.*[68]	US University students	741	39.4% reported lower binge drinking post campus closure while 4.18% reported higher 30 day binge drinking frequency post campus closure
Hooijdonk *et al.*[69]	Dutch University students	9967	Decrease in weekly binge drinking
Valente *et al.*[70]	Latin American and Caribbean adults	12,328	Increase in heavy episodic drinking amongst individuals with AUD
Morales *et al.*[71]	Mexican adults	9361	Poor mental health was found a predictor of increased alcohol use during COVID-19 pandemic
Weerakoon *et al.*[72]	US adults	1982	34% of the sample reported increased binge drinking. Increased binge drinking was seen among binge drinkers compared to non-binge drinkers
Vasconcelos *et al.*[73]	Portuguese college students	146	Decreased alcohol consumption in binge drinkers during lockdown

Abbreviations: AUD, Alcohol use disorder; AUDIT C, AUD Identification Test.

cirrhosis based on primary diagnosis. Most of these patients were males (71.45%), and non -Hispanic whites (59.80%) with 29% above 60 years of age. Higher incidence rates of hospitalizations were observed in males compared with females (IRR = 2.68, 95% CI: 2.21–3.71, $P < 0.01$), those between age 50–59 and 60–69 compared to over 70 years and among Native Americans and Hispanics. Another notable finding was a significant increase in the rates of hospitalization by approximately 20% in patients with alcohol associated cirrhosis from 2007 to 2014. Further stratification of the results showed this increase to be greater in females compared to males (33.5% increase in females vs. 14.7% increase in males, $P < 0.01$), and among Native Americans and Non-Hispanic whites compared to African Americans, Asian/Pacific Islanders and Hispanic patients. Mortality data from the same study demonstrated higher mortality rates among patients hospitalized with alcohol-associated cirrhosis compared to alcohol related hepatitis (6.98% compared to 2.97% respectively). Among patients with alcohol associated cirrhosis, higher mortality rates were observed in non-Hispanic whites compared to Hispanics (7.25% vs 5.95%, $P < 0.001$), with African Americans showing significantly higher odds of mortality on multivariate regression analysis ((1.13, 95% CI: 1.04–1.24, $P < 0.01$]). In addition, patients who were self-pay/uninsured showed higher in hospital mortality (OR = 1.506, 95% CI: 1.39–1.64, $P < 0.001$), in comparison to Medicare patient population (OR = 0.812, 95% CI: 0.75–0.87, $P < 0.001$). These differences in outcomes should be the focus of future studies to lessen these disparities and allow timely intervention to decrease mortality and morbidity in those with alcohol-associated cirrhosis.[37]

KEY POINTS

Based on observational studies, there has been a notable increase in the rates of hospitalizations in patients with alcohol associated cirrhosis with higher mortality rates seen in these patients compared to alcohol related hepatitis. Mortality rates have been particularly high in African American and non-Hispanic whites and those were self-pay/uninsured.

GLOBAL AND ECONOMIC BURDEN OF ALD

Global mortality and burden of alcohol-related liver disease are described as disability-adjusted life years. In 2016, chronic liver disease secondary to AUD resulted in 50% of the estimated 1,254,000 liver disease deaths ((588,100; 95% CI: 531,700–683,400; 46.9% of all liver disease, 95% CI: 42.4–54.5) for age groups of 15 years and above with men having a significantly higher number of deaths (416,700, 95% CI: 379,900–514,800) than women (171,400, 95% CI: 134,500–189,700). Based on the on disability-adjusted life years from 2016, 21.5 million years of life were lost due to ALD (21, 476, 000 DALYs; 95% CI: 19,448,000–24,811,000) with men again affected significantly more than women (men: 15, 568, 000 DALYs; 95% CI: 14, 230, 000–19,125,000; women: 5,909,000 DALYs; 95% CI: 4,653,000–6,423,000) with a major portion of these years of lives lost attributable to premature deaths rather than disability [38] In a health care claim analysis report, over 15,000 commercially insured adults with alcohol related hepatitis-related hospitalization from 2006 to 2013 were followed, with 2/3 of the adults dying over five years, and less than 500 receiving liver transplantation. Among those who survived, over 50% were hospitalized within one year and nearly 75% in the second year with total cost expenditure being estimated at $145,000 per patient. This cost burden decreased from about $50,000 in the first year to about $10,000 later. For those who underwent a liver transplant, total transplant-related costs averaged about $300,000, with total health care costs reaching up to $1,000,000 over five years and over five years, the total cost of care for the entire cohort was $2.2 billion.[33]

Other disparities in the US have been reported. Mortality rates for white women rose from the year 1990–2014, with heavy drinking as one of the major determinants with deaths from cirrhosis almost doubling amongst rural women in their early 50s by the end of the 20th century.[39] Another report from the National Academy of Sciences showed a rise in mortality among white non-Hispanic men with AUD related liver cirrhosis as the leading cause of mortality in these patients.[40]

KEY POINTS

Based on the on disability-adjusted life years from 2016, 21.5 million years of life were lost due to ALD with men again affected significantly more than women with a major portion of these years of lives lost attributable to premature deaths rather than disability. Based on health care claim analysis report, those who survived, over 50% were hospitalized within one year and nearly 75% in the second year with total cost expenditure being estimated at $145,000 per patient.

COVID-19 AND ALD

Patients with alcohol-associated liver disease have been affected by the COVID-19 pandemic both directly and indirectly (Figure 2). Before the COVID-19 pandemic, national data had shown an increasing trend in drinking and hence overall burden of AUD as previously discussed. This has culminated in an increase in the rates of hospitalizations, liver transplantation, cost, and mortality of patients with alcohol-associated liver disease.[41] As previously noted, higher mortality rates in women and younger adults have been observed prior to the pandemic with national death certificate data suggesting an average annual percentage change (AAPC) in mortality rate in women aged 25–34 years of 6.07 (2.95–9.28) compared to women age 65–74 years with AAPC 1.81 (95% CI 0.92–2.71).[42] Prior to COVID-19 pandemic, rates of pharmacotherapy and AUD counseling were estimated at 10–14% in patients with alcohol-associated cirrhosis, which indirectly correlates with higher rates of decompensation, mortality, readmission, and relapses in this patient population.[42,43]

The COVID-19 pandemic has resulted in a drastic increase in alcohol consumption worldwide.[44] Based on epidemiological data from US, alcohol use significantly increased in an early pandemic in the general population.[45] This surge in alcohol use directly correlated with the increase in online alcohol sales, which showed a spike to 477% in the US compared to previous years[46] Households with younger adults, young individuals, and ethnic minorities have shown increasing trends in alcohol purchase during and post COVID pandemic.[47] Data from Canada suggests a 38% increase in alcohol purchase during the COVID pandemic, mostly attributed to online sales in the year 2020 compared to 2019. The online purchase of alcohol significantly increased during this time period, given the lower cost of alcohol per unit and this trend is perilous for individuals with AUD.[42,48] Based on a telephone survey in the UK, 189 individuals with AUD were queried about their alcohol use during the COVID pandemic with 24% reporting an increase in alcohol use, while only 19% reporting a decrease in alcohol consumption.[49] Another finding during the COVID pandemic has identified women with increasing rates of alcohol use which were already accelerating prior to the pandemic. The probable explanation is related to increased workload, including family and child care responsibilities during mandated lockdowns, accompanied by increased work-related responsibilities due to increasing economic burden on women compared to men.[50]

KEY POINTS

The COVID-19 pandemic has resulted in a drastic increase in alcohol consumption worldwide. This culminated in an increase in the rates of hospitalizations, liver transplantation, cost, and mortality of patients with alcohol-associated liver disease.

Alcohol Use in Women During COVID-19

Alcohol use in women has been on the rise during the COVID pandemic with multiple preliminary studies

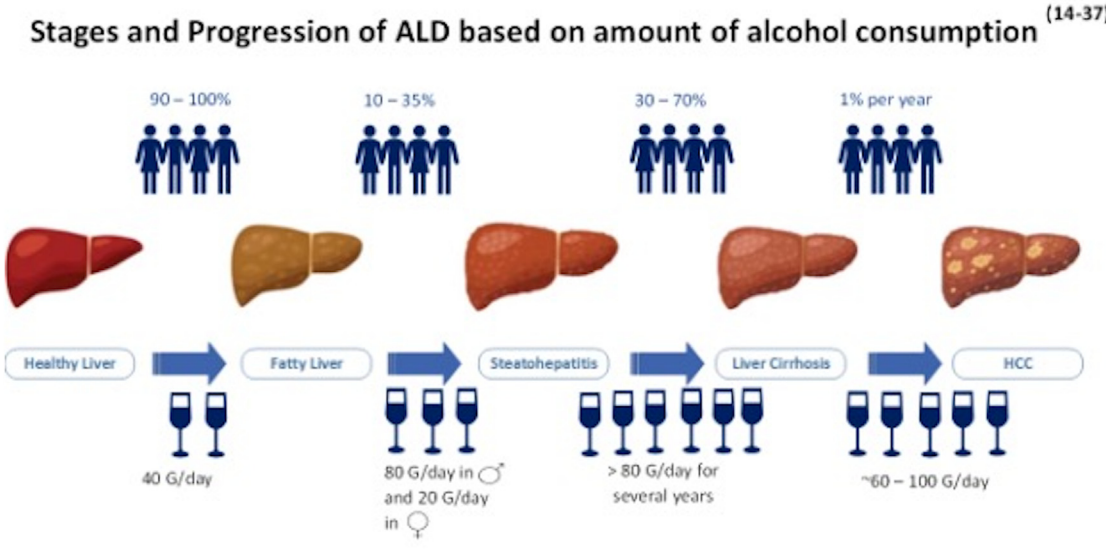

Figure 2 Stages and progression based on amount of alcohol consumption.

reporting increases in alcohol consumption in females. National surveys conducted before pandemic suggested an increase in AUD (AUD) in women. According to one study, 32% of women aged 15 and older consume alcohol worldwide. Another study reported an estimated increase of 6% in women aged 18 years and older who drank alcohol and about 14% whom binge drank.[51] The COVID-19 pandemic has not changed this trend. Preliminary results from the COLLATE project from Australia demonstrated an increased risk of drinking among women during the COVID-19 pandemic.[52] A small study conducted in Midwestern females in the US also confirmed an overall increase in alcohol use in women by 17%, and demonstrated an increase in AUDIT C (AUD Identification Test) scores. This increase was seen in both frequency and amount of alcohol consumed.[53] Another study reported about 34% of female participants binge drank in the previous month during the early days of the pandemic.[47] Additionally, an online survey of over 1000 young female adults in Poland found that 14.6% reported increased alcohol consumption in quarantine during the first wave of COVID-19 pandemic from April–May 2020.[54] Based on a survey study from Canada, the most common substance abused by pregnant females during the COVID-19 pandemic was alcohol, followed by Cannabis use, tobacco use, and illicit drugs. However, alcohol and substance use rates were comparable or lower than pre-COVID times in this population.[55]

Studies have demonstrated various risk factors for an increased risk of drinking among women during the COVID-19 pandemic. Based on a survey study of 417 participants with 83% female representation, a significant increase in the AUDIT C score from 3 to 4 was observed. In this study, 77% of females were married, and 44% were between the ages of 35 and 45. Significant determinants of increased AUD included having children at home, homeschooling, the closing of daycare centers, prior substance use disorder, and pressure for parental involvement[56] Jessica *et al.* investigated alcohol use in pregnant Alaskan Indian/Alaskan native females during the COVID-19 pandemic who were binge drinking prior to the pandemic. The study findings noted the persistence of binge drinking in these female participants, with those who reported less drinking being unmarried or with children sleeping in their rooms noted as protective factors[57] A significant increase in wait list additions and transplants for alcohol related hepatitis has been observed in preliminary reports, though gender-based rates of alcohol related hepatitis, listing, and liver transplants, and listing has not changed significantly during the COVID-19 pandemic compared to the pre-pandemic era.[58,59]

KEY POINTS

Alcohol use in women has been on the rise during the COVID pandemic with multiple preliminary studies reporting increases in alcohol consumption in females. This correlates with the reports of increase alcohol use in women before pandemic. Significant determinants of increased AUD during COVID-19 pandemic included having children at home, homeschooling, the closing of daycare centers, prior substance use disorder, and pressure for parental involvement.

PATTERNS OF ALCOHOL USE DURING DIFFERENT WAVES OF COVID-19 PANDEMIC

Multiple studies have reported on the use of alcohol during different waves of the COVID-19 pandemic (Table 3). In another study conducted in the UK during the first wave of the COVID-19 pandemic, there was an increase in alcohol consumption compared to other drugs and an increase in AUDIT C (AUDs Identification Test) scores was observed in these patients due to an increased frequency of alcohol use and not an increase in the number of drinks consumed. This increase in frequency of alcohol use was primarily seen in women and those with increased mental stress levels.[60] Another Belgian longitudinal study demonstrated differences in the use of alcohol intake during the COVID pandemic and various stages of lockdown. In their report, the onset of the lockdown was associated with a decrease in alcohol intake, while offsetting lockdown restrictions increased alcohol consumption. Younger individuals and those with AUD were affected by these changes. Protective factors for a reduction in alcohol use included fewer social gatherings, closure of restaurants, and increased awareness regarding alcohol use during the COVID-19 pandemic.[61] In another prospective study done in France during the third wave of the COVID-19 pandemic, a significant impact was seen on patients' drinking behavior with AUD with 50% of the patients reporting a significant impact of the COVID-19 pandemic on their drinking behavior. This was reflected in increased short-term drinking in these patients and increased psychological stress. The most critical risk factor associated with an increased risk of alcohol use was craving by multivariate analysis. An Israeli study demonstrated increased alcohol use in patients who experienced two lockdowns compared to those who experienced one lockdown. Interestingly, this pattern of increased alcohol use was not

seen with any other drugs of abuse during the COVID-19 pandemic. One explanation for increasing alcohol use may be related to reporting bias as it is legal to buy alcohol in Israel compared to other drugs of abuse.[62] In another study by Killgore *et al.*, a total of 5931 adults completed the AUDIT at one of the 6 time points from April through September 2020. Results demonstrated significant increase in heavy alcohol use over the period of 6 months with an upward trend in monthly alcohol use amongst those under COVID lockdown restrictions compared to those who were not under COVID-19 restrictions.[63]

Data from Australia have conflicting results on alcohol use during the COVID-19 pandemic with some studies reporting an increase in alcohol consumption, while others suggesting a potential decrease in consumption. An interrupted time series analysis performed in Australia suggested varying trends of alcohol use during the lockdown. Based on the data during the first and second wave, there was a decrease in premise-based alcohol consumption, while off-premises alcohol use remained unchanged. However, the removal of sheltering restrictions resulted in an abrupt increase in premise alcohol use. This variation in alcohol use mainly resulted from the closure of restaurants and bars while online alcohol purchase and at-home alcohol use remained unchanged.[64] One study noted an overall increase in the use of consumer credit cards by 20% in July 2020 compared to 2019, which was correlated with an increase in off-brand alcohol use in the early pandemic. Increasing alcohol purchase and online delivery sales of alcohol could reflect non-regulation of online purchases, increase in psychological distress, and mental stress during a pandemic. In contrast, another study demonstrated a potential decrease in alcohol use during the COVID-19 pandemic that might have resulted from the economic effects of the pandemic such as loss of job, decreased income, and psychological distress accumulation over time.[65] A Polish survey of 4072 individuals suggested an overall decrease in alcohol consumption during the pandemic compared to the pre-pandemic period. Subgroup analysis of the results from the study demonstrated an increase in the frequency of alcohol use in men, inhabitants of large cities, and remote workers.[66] An international study involving individuals from 83 different countries was conducted via an online survey to assess changes in drinking behavior before and during COVID-19 lockdown. While the study demonstrated an overall decrease in drinking behavior during the lockdown as demonstrated in some prior studies 36% of patients reported increased alcohol use including essential workers, individuals with children, those with relatives with COVID-19, depression, anxiety, and impulsivity.[67] A final study done from the Netherlands demonstrated an overall decrease in the weekly binge drinking patterns in Dutch university students, while cannabis use increased, and weekly smoking remained stable during the COVID-19 pandemic.[68]

KEY POINTS

Social isolation and increased psychological stress has been important determinants of short term increase in alcohol use during COVID-19 pandemic. Decrease in premise-based alcohol consumption was seen during the first and second wave of COVID-19 pandemic, however off premises alcohol use remained largely unchanged.

BINGE DRINKING DURING THE COVID-19 PANDEMIC

Data on college students, teenagers, and adults in different countries have provided insights on binge drinking during COVID-19 pandemic. In a study done on 741 first-year college students, binge drinking was reported in about 6.75% of the students while 39.41% reported decreased episodes of binge drinking after closure of the campuses. Those who reported lower binge drinking showed differences in coping, isolation, and underlying drinking motives, while those who reported more significant binge drinking were in fraternities/sororities and considered this level of drinking a norm.[69] Based on data from Dutch university students, weekly binge drinking decreased in students from 27.8% to 13.9% while smoking and cannabis use remained stable.[70] A cross-sectional online survey study involving 12,328 adults in 33 countries of Latin America and the Caribbean from Pan-American Health Organization data reported that 65% of drinkers from 2019 reported heavy alcohol drinking during the COVID-19 pandemic with 13.8% reported an increase in heavy alcohol drinking and 33.38% showing a decrease. Factors associated with increased heavy drinking during the pandemic included male gender, higher quarantine practice, and higher income status and generalized anxiety whereas living with children, being a student, and not being employed was associated with the decreased frequency of heavy alcohol use.[71] Similar to this report, data from a cross-sectional online survey from Mexico reported poor mental health as one of the factors leading to binge drinking and increased substance abuse.[72]

Multiple online surveys have been reported from the US. One online survey included 832 respondents and demonstrated an estimated increase in binge drinking of 34.1% of participants, with 7% reporting extreme binge

drinking. Patients who reported increased drinking also reported increased stress levels, increased alcohol availability, and boredom[47] In another self-reported survey from the US early in the pandemic, included 1982 participants from mid-March to mid-April 2020 with 34% of participants reporting binge drinking. There was an increased alcohol consumption seen in binge drinkers compared to non-binge drinkers with an association of increased time spent at home during the pandemic correlating with binge drinking (OR 1.19 (1.06–1.34). Depressive symptoms were also associated with increased alcohol.[73] In a study on Portuguese college students, it was reported that increased alcohol cravings and living with friends were crucial factors of alcohol use during the lockdown. Contrary to other studies, stress anxiety, and depression were not associated with the changes in drinking behavior.[74]

KEY POINTS

There has been mixed reports on binge drinking episodes in college students and teenagers during COVID-19 pandemic. Factors associated with heavy, or binge drinking included male gender, higher quarantine practice, psychiatric illness like anxiety or depression and higher income status.

Drinking Patterns and Correlation Between COVID-19 Pandemic and Great Recession in 2008

An interesting correlation of current data on alcohol use during the COVID-19 pandemic can be made to drinking patterns during the Great Recession in 2008. Though there was an overall decrease in the prevalence of alcohol use or any alcohol drinking during this time, there was a significant increase in binge drinking, which was statistically and epidemiologically significant with risk factors contributing to increased binge drinking including non-Black race, unmarried men under 30, and recent unemployment. Similar trends in alcohol use have been noted during COVID-19 pandemic. This polarization in drinking behavior stemmed from the fact that not all populations are equally affected. Two hypotheses have been proposed to explain the patterns of drinking and include the income hypothesis and provocation hypothesis. The income hypothesis implies that decreased alcohol consumption correlates with a decrease in income affecting mostly young and those with less education leading to less spending on alcohol and hence abstention. The provocation hypothesis is based on an increase in heavy or binge drinking episodes in those with job insecurity, unemployment, and threat of loss of life savings or home.[75]

Mortality Rates in Patients With AUD During COVID-19

COVID-19 infection has caused increased mortality in patients with AUD due to changes in immune response and severity of the acute respiratory syndrome with multiple factors contributing to the worse outcomes. Individuals with ALD have disrupted innate and acquired immune responses given chronic alcohol use which may result in increased severity of COVID-19 infection.[76] ALD patients also have decreased antioxidants in the lungs and changes in alveolar epithelial cells in addition to other comorbidities, including metabolic syndrome, chronic kidney disease, and tobacco use that are associated with worse COVID-19 outcomes. With regard to pre-existing liver disease, multicenter international registries have reported that those with decompensated alcohol cirrhosis, hepatocellular carcinoma, and ALD have worse outcomes with increased morbidity and mortality.[77,78]

Impact of COVID-19 Pandemic on Liver Transplantation in Alcohol-associated Liver Disease

The full impact of COVID on long-term alcohol intake patterns (rather than short-term changes) on 5-year and 10-year alcohol liver disease burden remains to be defined.[79] There are preliminary studies that have investigated the impact of COVID-19 on liver transplantation listing and liver transplantation. A retrospective cohort study using the UNOS database compared listing and rates of liver transplantation in alcohol-associated liver disease during the early pandemic to the pre-pandemic era. A total of 606 candidates with acute alcohol-associated liver disease were identified amongst 38,217 patients on the liver transplant waiting list from March 1, 2018, to February 28, 2021. A mean increase of 106.6% in rate of addition to the waiting list with 210.2% increase in receipt of liver transplants ($P < 0.001$) compared to the pre-pandemic era.[58] Another study examined temporal trends of LT during the COVID-19 pandemic, and demonstrated a significant increase in the rates of liver transplant listing and liver transplant related to ALD ($P < 0.01$) and was accompanied by an overall decrease in liver transplant listing for hepatitis C -related cirrhosis and nonalcoholic steatohepatitis though the total number of listings and

transplants remained unchanged. Not surprisingly young adults demonstrated the greatest increase in ALD, accounting for 33%, with severe ALD (alcohol related hepatitis) accounting for about ~50% of transplants and high acuity of illness with 40% having MELD score >30[59] The increase in alcohol related transplants during the COVID-19 pandemic only reflects a small fraction of alcohol-associated liver disease burden as <6% of patients who develop severe disease with alcohol-related hepatitis are listed for liver transplant.[80,81]

Ongoing Clinical Trials

Based on the data above, COVID-19 has significantly impacted alcohol use worldwide, especially in those with AUD. The short-term implications of the COVID-19 pandemic on AUD have been studied chiefly via survey analysis. Ongoing clinical trials are investigating the impact of COVID-19 on the drinking behavior of patients with underlying chronic liver disease (NCT04876443, NCT04375670). In addition, diagnostic and intervention studies investigating the outcome of behavioral intervention on AUD are also in progress (NCT05191446). These studies will help us better understand the natural history of alcohol use during a pandemic, insight into causative factors, and ways to mitigate the short-term and long-term effects of alcohol abuse in patients with and without underlying liver disease.

KEY POINTS

COVID-19 infection has caused increased mortality in patients with AUD and ALD. Though, preliminary studies have reported an increase in the total number of liver transplant listings and rates or liver transplantation in patients with ALD during COVID-19 pandemic, the increase in alcohol related transplants during the COVID-19 pandemic only reflects a small fraction of alcohol-associated liver disease burden as < 6% of patients who develop severe disease with alcohol related hepatitis are listed for liver transplant. Ongoing clinical trials are investigating the impact of COVID-19 on the drinking behavior of patients with underlying chronic liver disease in addition to outcomes of behavioral interventions on AUD.

ALD remains a significant public health issue world-wide, given an increase in the rates of advanced liver disease, including liver cirrhosis that has been observed world-wide and large disease burden with men having high rates of disability-adjusted life years lost. Advanced liver disease secondary to AUD causes a significant strain on health care systems in terms of overall cost, hospitalizations, and rates of liver transplantation in this patient population There has also been a substantial increase in morbidity and mortality rates in these patients, especially those with advanced fibrosis due to alcohol-associated liver disease. Based on results from a study on 3000 patients, only 3.8% of ALD patients are referred at early stages for intervention compared to 17% and 30% of patients with non-alcoholic fatty liver disease and viral hepatitis and earlier identification and intervention in those with early stage ALD will be required to reduce overall morbidity and mortality in this population globally.[82] In addition, the medical, social, and economic impacts of ALD have risen further since the onset of COVID pandemic with higher rates of binge drinking observed in selected groups and higher rates of listing and liver transplants for ALD. Individual and population-based strategies and policies are needed to counter the detrimental use of alcohol. While pharmacological and behavioral interventions remain the cornerstone of management at the individual level, specific public health policies for effective control of excessive alcohol use and its overall impact are needed. Future analyses and studies focusing on local regulations, socioeconomic and cultural factors influencing excessive alcohol use may be required to devise better policies at the population level to reduce alcohol-related mortality and morbidity effectively and thus reduce the global burden of disease.[83]

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Conceptualization was done by Dr. Kwo and Dr. Aslam. Literature search and original writing were done by Dr. Kwo and Dr. Aslam. Jointly the manuscript was edited and finalized.

CONFLICTS OF INTEREST

Paul Kwo, Advisory Board Durect, Surrozen. Stock Options Durect.

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