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Decreasing Cirrhosis Risk in MASLD: Don't Drink Alcohol!

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LIVER

This article reviews Wong RJ, Yang Z, Cheung R *et al*. Impact of longitudinal alcohol use patterns on long-term risk of cirrhosis among US veterans with steatotic liver disease. Gastroenterology 2024; 166(6):1156-1165.

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STRUCTURED ABSTRACT

Question: What is the impact of long-term alcohol use on risk of cirrhosis among U.S. veterans with metabolic dysfunction-associated steatotic liver disease (MASLD)?

Design: Retrospective cohort study

Setting: US veterans receiving care at all Veterans Affairs (VA) healthcare facilities between January 2010 and December 2017, with data captured in the VA Corporate Data Warehouse

Patients: Adult veterans aged >18 years with MASLD, based on the recent internationally-accepted definition. This requires presence of hepatic steatosis and 1 or more of the following metabolic comorbidities: 1) overweight or obese, defined as body mass index (BMI) >25 kg/m^2 in non-Asian people and >23 in

Asian people; 2) presence of diabetes, insulin resistance and/or use of anti-diabetes medications; 3) hypertension, blood pressure >130/85 mmHg and/or use of antihypertensive medications; 4) triglycerides >150 mg/dL, high-density lipoprotein (HDL) <40 mg/dL for men or <50 mg/dL for women and/or use of lipid-lowering medications. While the term MASLD does not encompass patients with significant alcohol use and/or possible concurrent alcohol-associated fatty liver disease (newly termed *metALD*), such patients were included in the study. Exclusion criteria included: 1) patients with known cirrhosis at baseline (including 12 months prior to MASLD diagnosis) or within 6 months after study entry; and 2) patients missing data on baseline alcohol use.

Outcomes: Primary outcome was development of incident cirrhosis, stratified by baseline alcohol use as defined by the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score. This survey is routinely conducted as standard of care at VA healthcare facilities. High-risk alcohol use was defined as AUDIT-C score $\geq$3 for men and $\geq$4 for women, low-risk alcohol use as AUDIT-C score 1-2 for woman and 1-3 for men, and no alcohol use defined as AUDIT-C = 0. Cirrhosis was defined using ICD-9/10 codes and previously published algorithms to identify cirrhosis in the VA Corporate Data Warehouse. Longitudinal changes in alcohol use were assessed based on changes in AUDIT-C score on follow-up assessment. The secondary outcome was median overall survival, stratified by alcohol use (none, low-risk, and high-risk) with censoring at date of death or liver transplant.

Data Analysis: Risk of cirrhosis was presented as incidence per 100 person-years, stratified by baseline alcohol use categories and other demographic and clinical factors. Multivariable competing risks Cox proportional hazards models were used to evaluate the association between alcohol use and risk of cirrhosis.

Funding: None reported.

Results: Overall, 1,156,189 veterans with steatotic liver disease (SLD) were identified, with 54.2% reporting no alcohol use, 34.6% with low-risk alcohol use, and 11.2% with high-risk alcohol use at baseline. Median follow-up time was 9.1 years (interquartile range [IQR] 5.8 – 12.0 years), 9.7 years (IQR 6.7 – 12.1) and 9.3 years (IQR 6.3 – 11.9) for the no alcohol, low-risk, and high-risk groups, respectively. Incidence of cirrhosis among patients with SLD and high-risk alcohol use was 0.76 per 100 person-years (PY) compared to 0.42 per 100 PY in the low-risk group and 0.53 per 100 PY in the no alcohol group ($P < 0.001$) (**Figure 1**).

This corresponded to a 43% higher incidence of cirrhosis among patients with high-risk alcohol use compared to those with no alcohol use. This finding was consistent across subgroups. Cirrhosis incidence was highest in the high-risk alcohol group among both men and women, and across all racial and ethnic groups. Among patients with high-risk alcohol use, the highest risk of cirrhosis was observed among Hispanic patients (0.90 compared to 0.78 per 100 PY for White patients, 0.70 per 100 PY for Black patients, and 0.47 per 100 PY for Asian/Pacific Islander patients), men (0.78 vs 0.43 per 100 PY for women), and adults aged 40-59 years (0.96 vs 0.26 per 100 PY for those aged >60 years and 0.70 per 100 PY for those aged 18-29 years).

Among patients with high-risk alcohol use, those that decreased their intake during follow-up had a 39% lower risk of cirrhosis compared to those who did not change their alcohol intake (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.45- 0.83). However, very few patients received either pharmacologic or behavioral therapy for alcohol use during the study period: 1.7% of the no alcohol group, 1.4% of the low-risk alcohol group and 5.0% of the high-risk alcohol group. No significant difference in survival was observed between the 3 groups.

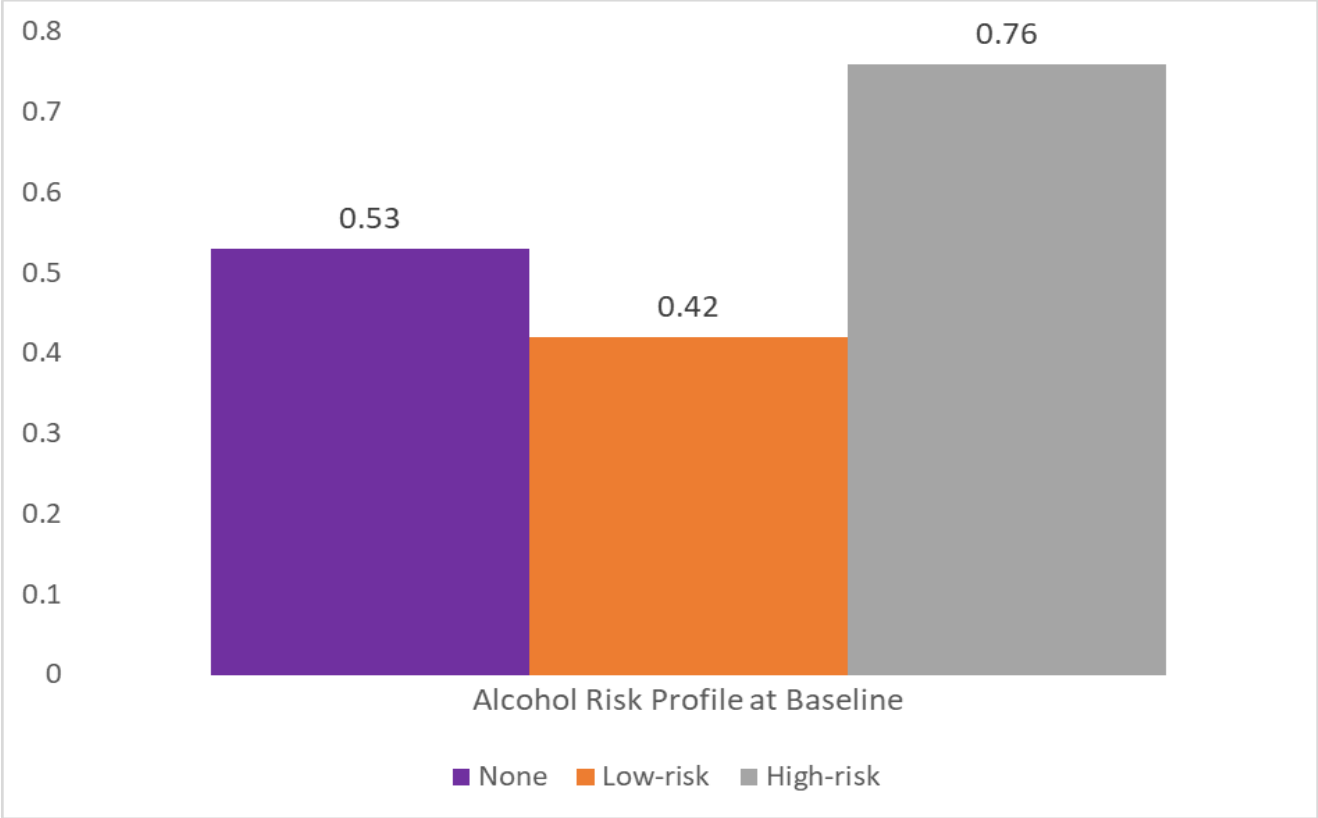

Figure 1: Cirrhosis incidence per 100 person-years.

COMMENTARY

Why Is This Important?

MASLD is now the most common liver disease globally and the fastest increasing indication for liver transplant in the US.[1,2] Alcohol use is also highly prevalent (and increasing in recent years[3]) among the general population in the US,[4] including those with SLD. It has been surmised that moderate to heavy alcohol use in patients with MASLD may lead to increased rates of (and more rapid) disease progression. However, data are conflicting on the magnitude of the impact of concurrent alcohol use on progression to cirrhosis and decompensating events (e.g., development of ascites, hepatic encephalopathy, variceal hemorrhage) among patients with MASLD. Further, most patients with MASLD and alcohol-related liver disease (ALD) are asymptomatic and only an estimated 20%-35% will progress to advanced fibrosis or cirrhosis.[5, 6] Accurate risk estimates are needed to quantify the harmful effect of alcohol in MASLD to better equip clinicians when counseling patients with this highly common condition about the risks of continued alcohol consumption and the benefits of abstinence.

This large, nationwide cohort study comprising >1.1 million patients with AUDIT-C survey data provides important data on the harmful impact of alcohol use in MASLD. Identification of patients with MASLD at higher risk of developing cirrhosis may help identify patients at greatest need of intervention, including linkage to care for behavioral and pharmacologic treatment of alcohol use disorder (AUD).

Key Study Findings

In a nationwide cohort of over 1.1 million veterans with steatotic liver disease, 1 in 9 patients reported concurrent high-risk alcohol use, which was associated with 43% higher risk of cirrhosis compared to those with low-risk or no alcohol use. Among patients with high-risk alcohol use, those that decreased their intake during follow-up had a 39% lower risk of cirrhosis compared to those who did not change their alcohol intake (HR 0.61, 95% CI 0.45-0.83).

Caution

The primary limitations of this study are those inherent to retrospective cohort studies, particularly the possibility of recall and misclassification biases. The AUDIT-C, which was used to risk stratify alcohol use in this study is self-reported and prone to recall bias. Additionally, the misclassification of MASLD is common and often results in patients with ALD being incorrectly diagnosed as MASLD when alcohol consumption is not disclosed or underestimated, as well as patients with "true" MASLD being incorrectly diagnosed as ALD. However, the results in this study were consistent after sensitivity analyses were performed excluding patients with AUDIT-C scores >8 and those

with an ICD-9/10 code for ALD. This study also used *International Classification of Diseases, Ninth/Tenth Revision* (ICD-9/10) codes to ascertain the outcome of incident cirrhosis which may also result in misclassification. Notably, there is no specific code for MASLD-associated cirrhosis; the new ICD-10 code for MASLD, K76.0, does not specify liver disease severity and/or presence of cirrhosis.

This study evaluated overall survival (which was similar between the 3 groups, possibly due to inadequate follow-up time) but did not assess the outcome of major adverse liver outcomes (MALO), an important clinical endpoint increasingly being reported in MASLD trials. Finally, we should remain cautious when generalizing this study's results to women and racial and ethnic minority groups given the predominantly male, non-Hispanic white veteran population.

My Practice

In my practice, in accordance with the 2019 AASLD Alcohol-Related Liver Disease and 2023 AASLD MASLD Practice Guidance documents, I advise patients with MASLD (and/or other chronic liver diseases) that any amount of alcohol, even mild or moderate use, has not been determined to be "safe" and advise complete abstinence.[7, 8] The AASLD also recommends that all patients in both inpatient and outpatient settings should be routinely screened for alcohol use with validated questionnaires, such as the AUDIT-C.[9] A nonjudgmental, compassionate and motivational interviewing approach can center the patient's concerns regarding alcohol cessation and treatment. For patients reporting unhealthy or hazardous alcohol use, I recommend counseling either online or in-person (e.g., Alcoholics Anonymous or other support groups) and offer referrals to behavioral health/psychiatry services for consideration of the full range of treatment options, including pharmacologic therapy. The study by Wong et al found that less than 5% of patients with MASLD receive treatment for alcohol use disorder, including those with high-risk alcohol use. Inadequate treatment of AUD among patients with chronic liver disease may partly result from the discomfort of primary care and gastroenterology/hepatology providers regarding prescribing relapse prevention medications and monitoring for their effectiveness and side effects. Integrated, multidisciplinary care models can improve ALD outcomes by addressing patients' medical, social and psychological concerns but are not widely available.[10]

I also counsel patients with MASLD, metALD and ALD on lifestyle modifications for healthy weight loss (when applicable) as well as behavioral, pharmacologic and surgical therapies for treatment of obesity. Patients should also be advised to consult with their primary care provider regarding diabetes control and cardiac risk factor modification.

For Future Research

Further studies are needed to confirm these results in other populations (including women and racial and ethnic minority groups). Moreover, improving our ability to distinguish between patients with MASLD, ALD and metALD (using the new nomenclature) will be crucial when assessing prognosis and the efficacy of therapeutics for these conditions in the future.

Conflicts of Interest

Dr. Rich has no relevant conflicts of interest.

Note: An author of this study are active on social media. Tag them to discuss their work and this EBGI summary.

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