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VIEWPOINT

Ongoing Alcohol Consumptions Counteracts the Benefits of Sustained Virological Response in Patients with Well Compensated Hepatitis C Cirrhosis: an Observational Study

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Article commented:

Vandenbulcke H, Moreno C, Colle I, Knebel JF, Francque S, Sersté T, *et al.*
Alcohol intake increases the risk of HCC in hepatitis C virus-related compensated cirrhosis: A prospective study.
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COMMENT

A summary of the study in the *Journal of Hepatology*

Liver fibrosis is an established risk factor for the development of hepatocellular carcinoma (HCC). It is also proven that alcohol is also associated with the development and progression of liver fibrosis and it is accelerated in the presence of chronic hepatitis C virus (HCV).[1-3] It is clinically sound that HCV eradication may stop the progression of cirrhosis but is unknown whether ongoing alcohol consumptions may counteract the beneficial effect of sustained virological response (SVR).

The timely paper by Vandenbulcke, *et al*.[4] studied the effect of SVR and alcohol consumption in the progression of well compensated cirrhosis and the risk of HCC. They accrued a prospective cohort from 2009 to 2015 of 192 Belgian patients with compensated hepatitis C cirrhosis, and followed them up for a median of 58 months. Cirrhosis was diagnosed by a combination of clinical parameters (e.g., imaging evidence of varices, nodular surface of the liver), elastography (value >14.6 kPa) or liver biopsy. They excluded prevalent HCC and decompensated cirrhosis. The primary outcome was incident HCC, new decompensation of cirrhosis and death. HCC was defined using non-invasive radiological criteria using contrast-enhanced imaging techniques or pathology findings. Decompensation of liver disease was defined by presence of ascites confirmed by ultrasound, variceal bleeding, spontaneous bacterial peritonitis, overt encephalopathy or a bilirubin level > 3 mg/dL. The main exposures of interest were hepatitis C treatment and alcohol use. Treatment modalities included pegylated interferon-α (PegIFN-α) and ribavirin (2009-2011), boceprevir or telaprevir with PegIFNα and ribavirin after 2011, and direct acting antiviral agent combination after 2014. SVR was defined by undetectable HCV RNA 24 weeks after the end of treatment with a lower limit of detection of 50 IU/mL or less. Alcohol exposure was quantified per patients' self-report.

Survival analyses were conducted using Kaplan-Meier curves and Cox proportional hazard ratios. Time-to-event was calculated from the date of enrollment to the date of first detection of HCC, decompensation of cirrhosis or death. HCC was considered a dominant event over decompensation of cirrhosis in patients developing both complications. They also performed competing risk analyses for all the outcomes studied. For example, in the examination for the risk of HCC, decompensation of cirrhosis or death from non-liver-related causes were treated as competing risks.

Out of the 192 participants, 118 (61%) were abstinent during the whole study period including 70 never drinkers. Among the 74 patients (39%) who consumed alcohol during follow-up, the median alcohol intake was 15 g/day

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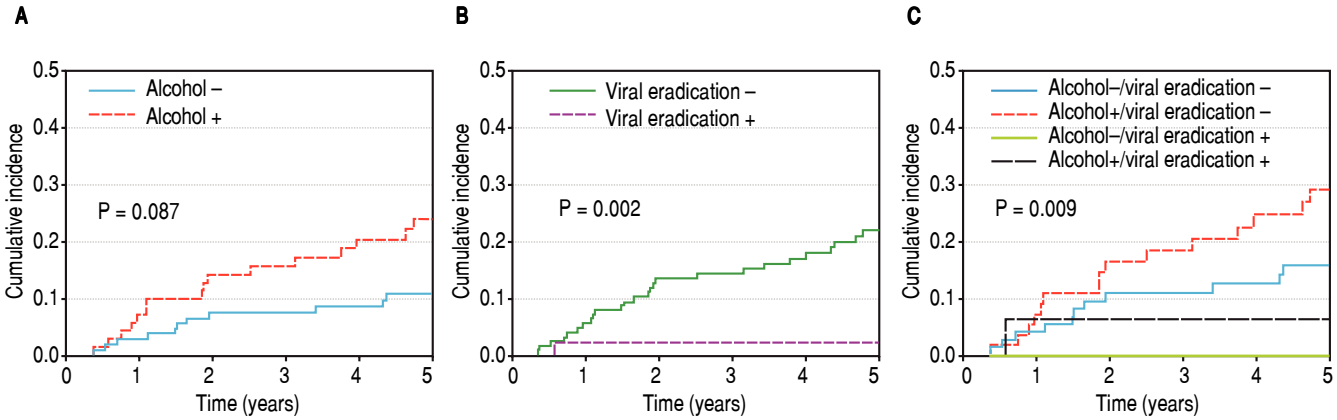

Figure 1. *5-year cumulative incidence rate of HCC.* ***A.*** *5 year cumulative incidence rate of HCC according to alcohol intake.* ***B.*** *5-year cumulative incidence rate of HCC according to viral eradication.* ***C.*** *5-year cumulative incidence rate of HCC according to alcohol intake and viral eradication. HCC: hepatocellular carcinoma. Kaplan Meier curves on the association between alcohol consumption and HCC, decompensation of liver disease and death. With permission from Elsevier.*

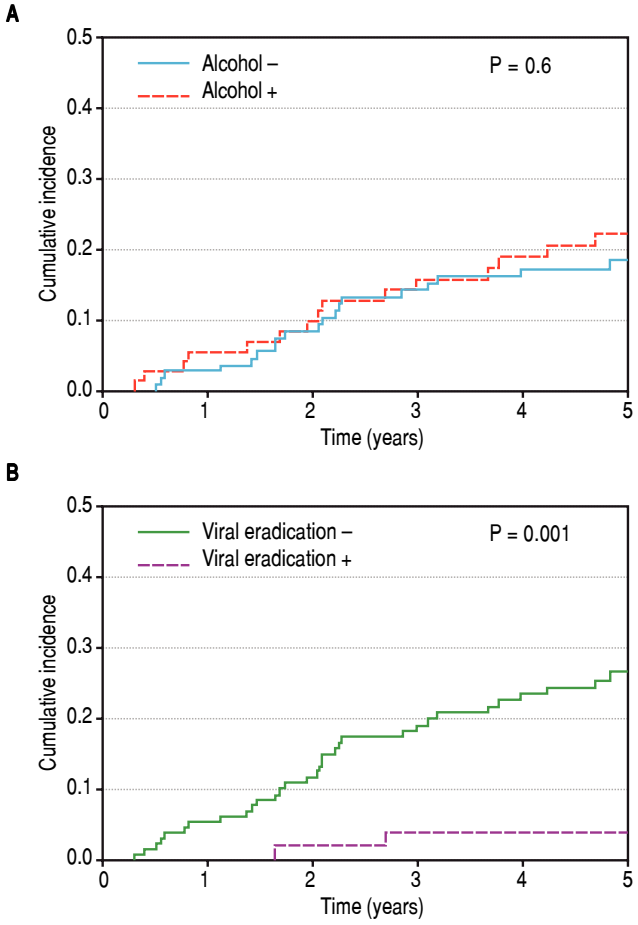

Figure 2. *5-year cumulative incidence rate of decompensation.* ***A.*** *5-year cumulative incidence rate of decompensation according to alcohol intake.* ***B.*** *5-year cumulative incidence rate of decompensation according to viral eradication. Kaplan Meier curves on the association between alcohol consumption and HCC, decompensation of liver disease and death. With permission from Elsevier.*

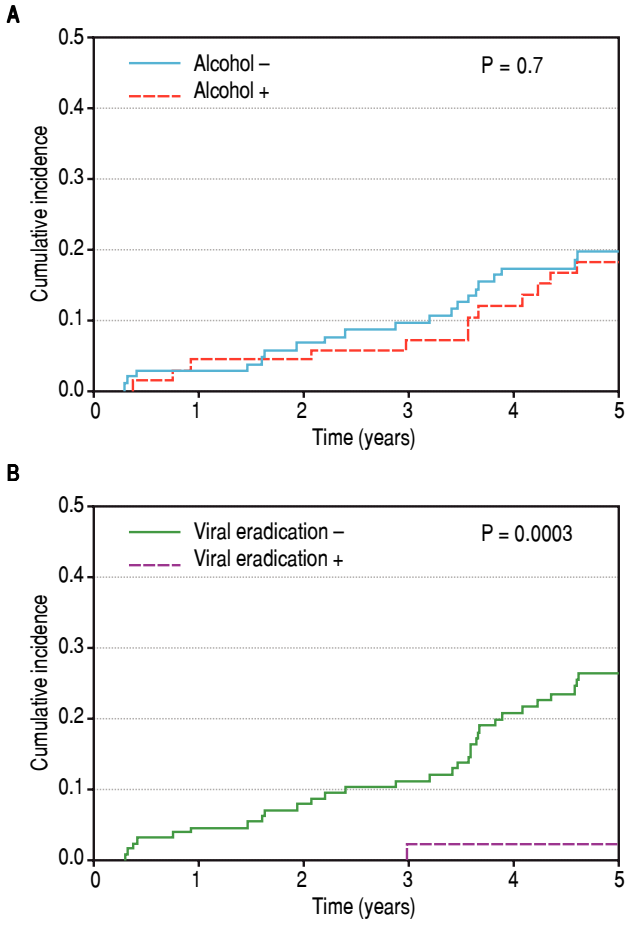

Figure 3. *5-year cumulative incidence rate of mortality.* ***A.*** *5-year cumulative incidence rate of mortality according to alcohol intake.* ***B.*** *5-year cumulative incidence rate of mortality according to viral eradication. Kaplan Meier curves on the association between alcohol consumption and HCC, decompensation of liver disease and death. With permission from Elsevier.*

(95%, confidence interval, CI: 5-20); 37 patients with alcohol intake <10 g/day, 15 with alcohol intake between 10 and 20 g/day, 7 with alcohol intake between 20 and 30 g/day and 15 with alcohol intake > 30 g/day. For analyses, they categorized as alcohol intake during the follow-up (yes *vs.* no) and the amount of alcohol intake during follow up (per 1-g/day increase). The majority of patients underwent antiviral treatment (166 patients, 86%, 29 were IFN free) and 68 reached SVR (35% of the entire study population).

Over time, the unadjusted survival analyses showed that SVR was associated with lower risk of HCC, decompensated cirrhosis and death. In contrast, alcohol intake (consumers *vs.* not consumers) was not associated with any of the outcomes. However, there was an interaction between SVR and alcohol where the lowest incidence of HCC was observed in participants who were not drinkers and also achieved SVR (Figures 1-3). In the multivariate analyses, alcohol intake during follow-up (yes *vs.* no) increased the risk of HCC compared to non-users (Hazard Ratio, HR 3.43, 95%CI: 1.49, 1.92) when adjusting for age, model of end-stage liver disease (MELD), platelet count, and viral eradication. For decompensated liver disease or death, neither consumption of alcohol *vs.* not or daily alcohol consumption was associated with either outcome.

The authors concluded that ongoing alcohol intake was an independent risk factor for incident HCC, in particular in patients without SVR. Because the median amount of alcohol intake was low in consumers (15 g/day, 95% CI: 5-20), they felt that light-to- moderate alcohol intake increases the risk of HCC in patients with active HCV and compensated cirrhosis encourage providers to stop alcohol use in these patients.

Why alcohol was not significant in most of the analyses?

The study by Vandenbulcke, *et al.* supports the synergism between alcohol and active HCV in affecting the risk of HCC. It is now a fact that SVR is beneficial to patients with hepatitis C and should be offered unless major contraindications exist. However, it was surprising that alcohol consumption was not associated with HCC and decompensated cirrhosis, independent of the coding used (continuous, dichotomous or categorical). Similar to other epidemiological research in alcohol, the reader would expect to see a significant, positive association with alcohol use in different categories, or perhaps, a J-shape association. In contrast, the only significant association was found after a *post-hoc* decision to collapse drinkers vs. non drinkers. Why is this happening? It is quite likely due to a systematic error (bias) associated with alcohol quantification in the study.

Measurement of alcohol consumption in epidemiological studies is challenging for several reasons. First, it lacks of gold-standard, as none of the available biomarkers (e.g., serum carbohydrate-deficient transferrin, urine ethyl glucuronide and ethyl sulfate, etc.) can estimate long-term alcohol use. Chronic alcohol use relies on patients' self-report which may introduce several types of information biases. Second, there are several standardized questionnaires for alcohol exposure (see below) that should be carefully selected depending on the aim of the study. And finally, alcohol exposure is subject to measurement error due to variations in alcohol content in drinks. In general, self-reported alcohol use has been shown to be underreported at a population level.[5]

Vandenbulcke, *et al.* found a low median alcohol consumption (15 g/day), compared to the traditional 30 g/day threshold for 10 years reported by Bellentani and Tiribelli,[6] was associated with progression of liver disease. Underreporting of alcohol use likely plays a role in both prior and current users, and the overall direction of the association between alcohol and liver outcomes is directed towards the null, i.e., no effect or non-differential misclassification.

Secondly, the lack of standard questionnaire increases the chance of null associations in the relationship between alcohol and hard outcomes in cirrhosis. In the absence of gold standard, validated alcohol questionnaires provide the best tool in clinical/epidemiological research to detect changes over time and provide content validity. For example, the alcohol timeline followback (TLFB) assesses daily and past drinking; the Form 90 gives an individual estimate of features of drinking in the last 90 days before last drink; the drinking self-monitoring log (DSML) gives advice and feedback during treatment and monitor progress; lifetime drinking history (LDH) provides information about lifetime drinking patterns, whereas quantity frequency (QF) measures, gives rapid information of the number of days drinking.

Finally, there are variations in the pattern of alcohol consumption between countries but also between drinkers.[7] The approach of Vandenbulcke, *et al.* did not differentiate between binge drinking and steady use. If any of these participants had evidence of alcoholic hepatitis in the setting of binge drinking as compared to steady use, these patients would have scored as low average alcohol consumer while being at high risk to develop complications of liver disease.[8]

Another reason for null effects: lack of power or model building

The authors conducted several multivariate analyses adding 5 to 6 potential confounders/covariates in the model for HCC (n = 33 events), decompensation (n = 53

events) or death (n = 39 events). Using the common guidance of a minimum of 10 outcome events per predictor variable, the study was likely to be underpowered.[9] A better approach could have been to rely less on selection of predictors based on p-values and put more weight on clinical reasoning/literature review while keeping in mind the small number of events.[10]

Recent studies support that triad alcohol and lack of SVR is bad for liver outcomes

Ganne-Carrie, *et al.* published a score to predict the development of HCC in patients with compensated HCV cirrhosis.[11] Using the French Multicenter ANRS CO12 CirVir cohort between March 2006 and July 2012, the authors studied 1,080 patients (720 assigned to training set and 360 to the validation set). Alcohol consumption was defined as excessive following the World Health Organization criteria (more than 2 glasses per day for females and more than 3 glasses per day for males); an overall minimal duration of 5 years was required. During a median follow-up of 51.0 months, a diagnosis of HCC was established for 142 patients. Past excessive alcohol consumption was associated with an increased risk of 55% for the development of HCC in well compensated HCV cirrhosis (HR: 1.55, 95%CI: 1.02, 2.36), when adjusting for clinically significant variables (age > 50, platelet count in three categories [< 100 10^3/mm^3; 100-150; and > 150 10^3/mm^3, GGT (IU/L) ≥ upper limit normality, or non-SVR during the study period). The authors concluded that using a 5 variable model, including past excessive alcohol intake, was accurate in the discrimination of HCC for 1 and 3 years predictions as shown in the area under the receiver operating characteristic curve (AUROC, 0.68 [0.55-0.80] and 0.72 [0.66-0.77], respectively).

van der Meer using individual data of 1,000 patients included in Western cohort studies with chronic HCV therapies, followed for 5.7 years. Fifty-one patients developed HCC and 101 had clinical disease progression.[12] The cumulative 8-year HCC incidence was 1.8 (95%CI 0.0-4.3) among patients with bridging fibrosis and 8.7% (95%CI 6.0-11.4) among those with cirrhosis. In contrast to Ganne-Carrie, *et al.*[11] history of alcohol abuse was not associated with HCC or clinical disease progression in the current cohort. The authors offered few factors to explain the lack of association: the heterogeneity of the gathered data or missing data or indication bias, that is may be partly responsible for these lacking associations. It should also be considered that all included patients underwent interferon-based therapy which is not generally administered to those with severe alcohol abuse. However, the authors pointed out that "It may be expected, however, that continuous alcohol abuse increases the risk of cirrhosis-related complications among patients with advanced liver disease and SVR as well, so that also these patients should be advised to limit their alcohol intake".

Take home points

How should the reader interpret the findings from the study of Vandenbulcke, *et al*.? With caution! There is no question that SVR will provide more protection for development of HCC compared to their non SVR counterparts. There is also no doubt that alcohol consumption is deleterious in patient with fibrosis as shown previously.[1-3] However, the exact effect size of alcohol on hepatitis C patients with and without SVR is unknown based on the current study because important limitations in the exposure measurement and small number of events.

We have several recommendations for future research on the interaction between hepatitis C, alcohol and liver disease. First, if alcohol recording is based on self-report:

- Ascertain that participants are alcohol free when interviewed.
- Give written assurances of confidentiality;
- Interview in a setting that encourages honest reporting (e.g., clinical or research *vs.* probation office);
- Ask clearly worded objective questions (e.g., "How many times have you been arrested for drunk driving?") *vs.* subjective questions (e.g., "Did you get drunk last night?"); and
- Provide memory aids (e.g., calendar for aiding recall of drinking).[13]

Second, to overcome limitations of power, future research would need individual patient data (e.g. van der Meer[12]) or meta-analysis with an attempt to standardize alcohol usage among participants. Finally, model building should explore linear and non linear associations between alcohol, hepatitis C and hard outcomes.

To conclude, what should the reader tell to a well compensated hepatitis C cirrhotic patient if he/she asks "how much can I safely drink"? The answer we believe is two-fold: close to zero, and let's start you on direct antiviral agent.

ABBREVIATIONS

- **AUROC:** area under the receiver operating characteristic curve operating.
- **CI:** confidence interval.
- **DSML:** drinking self-monitoring log.
- **HCC:** hepatocellular carcinoma.
- **HCV:** chronic hepatitis C virus (HCV).

- **HR:** hazard ratio.
- **LDH:** lifetime drinking history.
- **MELD:** model of end-stage liver disease.
- **PegIFNα:** pegylated interferon-α.
- **QF:** quantity frequency.
- **SVR:** sustained virological response.
- **TLFB:** alcohol timeline followback.

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