Research Article

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Alcohol intake increases the risk of HCC in hepatitis C virus-related compensated cirrhosis: A prospective study

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Background & Aims: Whether alcohol intake increases the risk of complications in patients with HCV-related cirrhosis remains unclear. The aim of this study was to determine the impact of alcohol intake and viral eradication on the risk of hepatocellular carcinoma (HCC), decompensation of cirrhosis and death.

Methods: Data on alcohol intake and viral eradication were prospectively collected in 192 patients with compensated HCV-related cirrhosis.

Results: 74 patients consumed alcohol (median alcohol intake: 15 g/day); 68 reached viral eradication. During a median follow-up of 58 months, 33 patients developed HCC, 53 experienced at least one decompensation event, and 39 died. The 5-year cumulative incidence rate of HCC was 10.6% (95% CI: 4.6–16.6) in abstainers *vs.* 23.8% (95% CI: 13.5–34.1) in consumers ($p = 0.087$), and 2.0% (95% CI: 0–5.8) *vs.* 21.7% (95% CI: 14.2–29.2) in patients with and without viral eradication ($p = 0.002$), respectively. The lowest risk of HCC was observed for patients without alcohol intake and with viral eradication (0%) followed by patients with alcohol intake and viral eradication (6.2% [95% CI: 0–18.4]), patients without alcohol intake and no viral eradication (15.9% [95% CI: 7.1–24.7]), and patients with alcohol intake and no viral eradication (29.2% [95% CI: 16.5–41.9]) ($p = 0.009$). In multivariate analysis, lack of viral eradication and alcohol consumption were associated with the risk of HCC (hazard ratio for alcohol consumption: 3.43, 95% CI: 1.49–7.92, $p = 0.004$). Alcohol intake did not influence the risk of decompensation or death.

Conclusions: Light-to-moderate alcohol intake increases the risk of HCC in patients with HCV-related cirrhosis. Patient care should include measures to ensure abstinence.

Lay summary: Whether alcohol intake increases the risk of complications in patients with HCV-related cirrhosis remains unclear. In this prospective study, light-to-moderate alcohol intake was associated with the risk of hepatocellular carcinoma in multivariate analysis. No patients who did not use alcohol and who reached viral eradication developed hepatocellular carcinoma during follow-up. The risk of hepatocellular carcinoma increased with alcohol intake or in patients without viral eradication and was highest when alcohol intake was present in the absence of viral eradication. Patients with HCV-related cirrhosis should be strongly advised against any alcohol intake. Patient care should include measures to ensure abstinence.

Keywords: Alcohol intake; Cirrhosis; Decompensation; Hepatocellular carcinoma; Survival; Viral eradication.

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Abbreviations: BASL, Belgian Association for the Study of the Liver; BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; INR, international normalized ratio; MELD, model for end-stage liver disease; PegIFN, pegylated interferon; SVR, sustained virological response.

Introduction

Chronic hepatitis C virus (HCV) infection is a major public health problem. HCV infects an estimated 130–170 million persons

worldwide and is responsible for 350,000–500,000 deaths per year [1,2]. It is one of the main causes of hepatocellular carcinoma (HCC) and the most common indication for liver transplantation in many European countries. When cirrhosis has developed, HCC and decompensation of cirrhosis occur at an annual incidence of 4 to 5% [3,4].

The progression of chronic HCV infection depends on several host and environmental factors. Among them, heavy alcohol intake is a well-known cofactor increasing the risk of cirrhosis, decompensation of cirrhosis, HCC and death in patients with chronic HCV infection [5–8]. Previous studies have, however, failed to identify a threshold level of alcohol consumption associated with an increased risk of complications or death. In 2000, Thomas *et al.* did not identify moderate alcohol intake as a risk factor for end-stage liver disease despite having followed more than 1,000 HCV patients for an average of 8 years [9]. Similar results were observed by others [4]. In a further cohort study, light-to-moderate alcohol consumption was not an independent risk factor associated with advanced liver disease or liver-related death [10]. On the other hand, one study found a synergistic effect of HCV infection and the consumption of less than 40 g of alcohol per day with the development of HCC [11]. Thus, whether light-to-moderate alcohol intake increases the risk of complications in patients with HCV-related cirrhosis remains unclear.

The primary objective in the management of HCV infection is viral eradication since patients with sustained virological response (SVR) generally do not experience fibrosis progression and show long-term improvement [7,8,12–15]. However, data on the benefit of viral eradication in patients with advanced disease are limited. Some studies indicate that SVR is associated with better survival in patients with extensive fibrosis or cirrhosis [16–18], but few studies specifically focus on cirrhotic patients [18–20]. Available data indicate that patients with HCV-related cirrhosis are still exposed to a risk of HCC after having reached viral eradication [21,22]. In addition, patients with SVR are exposed to a higher risk of death from liver-related causes than non-infected people [23].

To the best of our knowledge, studies focusing on the interactions between alcohol intake and viral eradication on the outcome of patients with HCV-related cirrhosis have not yet been published. In this study, we sought to determine the impact of alcohol intake and viral eradication on the risk of complications in patients with HCV-related cirrhosis. To do so, we prospectively followed a population of HCV patients with compensated cirrhosis. We collected data related to alcohol intake and viral eradication, as well as data related to the occurrence of HCC, decompensation of cirrhosis and death.

Materials and methods

Patients

In 2009, the Belgian Association for the Study of the Liver (BASL) launched a national register of patients with HCV-related cirrhosis. Patients were included only if they fulfilled the following criteria: (1) age older than 18 years; (2) cirrhosis related to chronic HCV infection; (3) cirrhosis demonstrated by a liver biopsy showing fibrotic nodules consistent with a METAVIR F4 fibrosis stage or by a transient elastography value >14.6 kPa or by unequivocal signs of cirrhosis (dysmorphic liver, esophageal or gastric varices); (4) compensated cirrhosis defined as Child-Pugh class A; (5) no previous complications attributed to cirrhosis. In addition, patients who developed HCC or decompensation within 3 months of their inclusion were excluded from the analysis. Patients who tested positive for hepatitis B surface antigen (HBs Ag) or for antibodies to human immunodeficiency virus were also excluded.

The study was approved by the leading Ethical Committee of CUB Hospital Erasme (Ref. P2008/235) and by the Ethical Committee of each participating centre. All patients gave their written informed consent.

Collection of data

At inclusion, data collected included past medical history (mode and year of HCV contamination, presence of esophageal varices, history of previous complications of cirrhosis, past alcohol and tobacco use, presence of diabetes, previous antiviral treatment history and previous treatment response), demographic data (gender, age, race, size, weight), clinical data (current alcohol and tobacco use, presence of ascites and of encephalopathy), biological data (alanine transaminase (ALT)) categorized as normal or between 1–2, 2–3, or >3 times the upper limit of normal, bilirubin, albumin, creatinin levels, prothrombine time or international normalized ratio [INR], platelet count), virological data (HCV genotype, HCV RNA, presence of other viral infections), histological data (presence of fibrotic nodules consistent with a METAVIR F4 fibrosis stage), and results of liver stiffness measurement.

During follow-up, patients were followed as outpatients every six-months, or more frequently if required. Data collected included clinical data (current alcohol and tobacco use, presence of ascites and presence of encephalopathy), biological data (ALT categorized as normal or between 1–2, 2–3, or >3 times the upper limit of normal, bilirubin, albumin, creatinin levels, prothrombine time or INR), and data related to the development of complications of cirrhosis, or to the occurrence of liver transplantation or death. HCV RNA was determined when patients received antiviral treatment for the assessment of virological response. Examination by Doppler ultrasonography was performed every 6 months for HCC surveillance.

Liver fibrosis assessment

Liver fibrosis was assessed by histology or non-invasive methods. A sample of each biopsy was used for histological examination by light microscopy. Liver biopsy sections were formalin-fixed, paraffin-embedded and routinely stained with hematoxylin-eosin. Specimens were evaluated according to the METAVIR score [24]. Transient elastography (FibroScan®, Echosens, Paris, France) is a rapid, non-invasive and reproducible method for measuring liver stiffness considered as an index of the amount of fibrotic tissue [25]. A value >14.6 kPa was considered indicative of cirrhosis [25,26].

Antiviral therapy and virological studies

Patients eligible for treatment received antiviral therapy according to guidelines and access to reimbursement of antiviral treatments in Belgium in effect during the time of the study. Hence, patients were treated with pegylated interferon-α (PegIFNα) and ribavirin. After 2011, patients infected with HCV genotype 1 were eligible for antiviral treatment combining boceprevir (VICTRELIS®; MSD) or telaprevir (INCIVO®; Janssen) with the previous bitherapy (PegIFNα and ribavirin). After 2014, patients were also eligible for PegIFNα, ribavirin and another direct acting antiviral agent combination therapy, or for an IFN-free treatment. Patients were assigned to receive treatment for 12–48 weeks depending on the schedule of treatment. 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 quantification

Past and current alcohol intake was assessed in detail at the time of the first visit and at each following visit. The assessment of alcohol consumption was made according to patient declarations and not through the use of a standard questionnaire. Beer, wine and liquor consumption were quantified individually through the description of each patient for typical quantity, frequency and duration of use. Years of consumption for each of the 3 alcohol types were estimated. We assumed that each drink contained the equivalent of 10 g of pure ethanol.

Study outcomes

The primary end-points were the development of HCC, decompensation of cirrhosis and death. Diagnosis of HCC was made by non-invasive radiological criteria using contrast-enhanced imaging techniques showing contrast uptake in the arterial phase and washout in the venous phase (one imaging technique in nodules >2 cm and two coincidental techniques in nodules of 1–2 cm in diameter) or

by histological examination. Decompensation was defined as any of the following events: presence of ascites confirmed by ultrasound, variceal bleeding, spontaneous bacterial peritonitis defined in accordance with the recommendations of the International Club of Ascites [27], overt encephalopathy or jaundice with a bilirubin level >3 mg/dl. The secondary endpoint was liver-related death. Deaths due to HCC or decompensation were considered as liver-related. All other causes of deaths were considered non-liver-related.

Statistical analysis

Data were expressed as percentage or median (95% CI). Analyses were conducted using variance analysis, the chi-square test, two-sided Fisher exact test, Mann-Whitney *U* test, Wilcoxon test and two-sample Student's *t* test when appropriate. Follow-up started at patient enrollment time. Data from patients still alive at the end of the study period were censored at the time of last contact or on December 31 2015, whichever came earlier. Time-to-event was calculated from the date of enrollment to the date of first detection of HCC, decompensation of cirrhosis or death. The following strategy was used in the assessment of events. Only the first episode of decompensation of cirrhosis or HCC was taken into account. HCC was considered a dominant event over decompensation of cirrhosis in patients developing both complications. We used cumulative incidence functions to describe the probability of an endpoint at a given time, as recommended [28]. The risk of HCC was described taking into account decompensation of cirrhosis or death from non-liver-related causes as competing risks. The risk of decompensation of cirrhosis was described taking into account HCC or death from non-liver-related causes as competing risks. The risk of overall death was estimated taking into account liver transplantation as competing risk. The risk of liver-related death was estimated taking into account death from non-liver-related causes and liver transplantation as competing risks. The Gray's test was used to test the cause-specific differences [29]. Average annual rates were estimated as numbers of events divided by the number of person-year at-risk. All results were reported with their 95% confidence interval (95% CI).

We assessed the impact of viral eradication on the occurrence of HCC, decompensation of cirrhosis, death and liver-related death as follows. First: viral eradication was considered to be a variable that could change over time. For patients receiving antiviral treatment and reaching SVR, observation time was censored when successful antiviral treatment was ended. This choice was justified by the fact that SVR patients were all HCV RNA–negative at the end of a successful antiviral treatment. As previously performed in another study [17], patients having reached SVR were considered as non-SVR patients until the end of the successful treatment, and thereafter as SVR patients until the end of the follow-up. Second: the association between viral eradication and each endpoint was tested in univariate analysis and, when the p value was <0.1, also in multivariate analysis.

We conducted univariate analyses and multivariate Fine and Gray proportional hazards models to identify factors associated with HCC, decompensation or death. Only covariates with a p value of less than 0.10 in the univariate analysis were included in the multivariable model. To avoid bias related to the effect of colinearity, when Child-Pugh or MELD scores were included in multivariate analysis, their constituent variables were not considered. Hazard ratios (HR) were reported with 95% CIs. All tests were two-tailed and a p value of less than 0.05 was considered to be statistically significant.

Univariate analyses were performed using NCSS 2007 software (NCSS, Kaysville, UT, USA). Fine and Gray proportional hazards models and cumulative incidence function were analysed using Anaconda 2.7 a free distribution of the Python programming language (Python Software Foundation. Python Language Reference, version 2.7.), the python module Rpy2 (Available at: https://pypi.python.org/pypi/rpy2) to link python with R 3.1.3 (R Core Team (2015), R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: http://www.R-project.org/.) and the R library "cmprsk" (Bob Gray (2014). cmprsk: Subdistribution Analysis of Competing Risks. R package version 2.2-7. Available at: http://CRAN.R-project.org/package=cmprsk).

Results

Study population

From January 2009 to December 2010, 257 consecutive patients with HCV-related cirrhosis were screened in 15 centres (Supplementary Table 1). 18 patients were excluded because they were HBs antigen positive or because they had antibodies against human immunodeficiency virus (n = 6), or because Child-Pugh score was >6 (n = 12). An additional 47 patients were excluded because no follow-up data were available or because HCC or decompensation occurred before or within the first 3 months after inclusion. Thus, 192 patients were included. The diagnosis of cirrhosis was made by liver biopsy in 111 cases, and by transient elastography or presence of unequivocal signs of cirrhosis in 81 cases. Patients for whom the diagnosis of cirrhosis was made with a liver biopsy were younger, were treated more frequently, and reached viral eradication more often than patients for whom the diagnosis of cirrhosis was made without a liver biopsy. Otherwise, the main characteristics did not differ according to the realization of a liver biopsy. Median follow-up was 58 months (95% CI: 54–60). Table 1 shows the characteristics of the 192 patients included.

Among these 192 patients, 118 (61%) were abstinent from alcohol consumption during the whole study period, 48 of these were past drinkers. Among the 74 patients (39%) who consumed alcohol during follow-up, the median alcohol intake was 15 g/day (95% CI: 5–20). There were 37 patients with alcohol intake $\leqslant$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 $\geqslant$30 g/day. 166 patients (86%) underwent antiviral treatment (which was interferon-free in 29 cases) and 68 reached SVR (41% of the patients who received an antiviral treatment, 35% of the entire study population). Of these, 18 patients already had viral eradication at inclusion and 50 achieved viral eradication during the follow-up period.

HCC, decompensation, death and causes of death

Clinical events occurring during the study period are reported in Table 2.

33 patients (17%) developed HCC, 16 out of 118 abstainers (14%) and 17 out of 74 consumers (23%) (p = 0.09). The diagnosis of HCC was made using radiological criteria in 21 cases and through a liver biopsy in the 12 remaining cases. Among consumers, patients who developed or who did not develop HCC had a median alcohol intake of 10 and 20 g per day (p = 0.6), respectively. Hence, drinking alcohol, not the amount of alcohol intake, was associated with an increased risk of HCC. Thus, all analyses were performed in abstainers and in consumers irrespectively of the amount of alcohol consumed. 7 out of 68 patients with viral eradication (10%) and 26 out of 124 patients without viral eradication (21%) developed HCC (p = 0.06). Tobacco use was not associated with the occurrence of HCC, even in consumers.

53 patients (28%) developed at least one decompensation event, 32 out of 118 abstainers (27%) and 21 out of 74 consumers (28%) (p = 0.8). 10 out of 68 patients with viral eradication (15%) and 43 out of 124 patients without viral eradication (35%) developed decompensation of cirrhosis (p = 0.003).

39 patients (20%) died. Cause of death was liver-related in 28 patients and non-liver-related in 11 patients. 20 patients underwent a liver transplantation (10%), 13 for HCC and 7 for decompensation of cirrhosis. 24 out of 118 abstainers (20%) and 15 out of 74 consumers (20%) died (p = 1.0). Among abstainers, cause of death was HCC in 4 cases (17%), decompensation of cirrhosis in 12 cases (50%), and non-liver-related in 8 cases (33%). Among consumers, cause of death was HCC in 5 cases (33%), decompensation of cirrhosis in 7 cases (47%), and non-liver-related in 3 cases (20%).

Table 1. Characteristics of the study population according to alcohol intake and viral eradication.

Characteristics	Overall (n = 192)	Abstainers (n = 118)	Consumers (n = 74)	*p* value	With viral eradication (n = 68)	Without viral eradication (n = 124)	*p* value
Age (yr)*	59 (55-62)	62 (58-66)	54 (51-58)	0.002	60 (55-62)	58 (55-65)	0.3
Sex ratio (No. of males, %)	117 (61%)	59 (50%)	58 (78%)	<0.001	45 (66%)	72 (58%)	0.3
Diabetes (No. %)	53 (28%)**	39 (34%)	14 (19%)	0.03	17 (26%)	36 (29%)	0.6
BMI (kg/m²) *	26 (26-27)	27 (26-28)	26 (25-27)	0.05	27 (26-28)	26 (25-27)	0.7
Genotype 3 (No. of HCV-3, %)	11 (6%)***	5 (4%)	6 (8%)	0.3	2 (3%)	9 (7%)	0.2
Past alcohol consumption (No. of consumers, %)	112 (60%)****	48 (42%)	64 (89%)	<0.001	38 (57%)	74 (62%)	0.5
Tobacco use (No. of consumers, %)	50 (29%)*****	21 (19%)	29 (43%)	<0.001	15 (23%)	35 (32%)	0.2
Bilirubin levels (mg/dl)	0.8 (0.7-0.9)	0.8 (0.7-0.9)	0.7 (0.6-0.8)	0.8	0.7 (0.6-0.8)	0.8 (0.7-1.0)	0.09
INR	1.1 (1.1-1.1)	1.1 (1.1-1.2)	1.1 (1.0-1.1)	0.12	1.1 (1.1-1.2)	1.1 (1.1-1.1)	0.3
Albumin levels (g/dl)	4.1 (4.0-4.1)	4.0 (3.8-4.1)	4.2 (4.0-4.4)	0.001	4.1 (4.0-4.3)	4.0 (3.9-4.1)	0.03
Creatinin levels (mg/dl)	0.8 (0.8-0.8)	0.8 (0.8-0.9)	0.8 (0.8-0.8)	0.4	0.8 (0.7-0.8)	0.8 (0.8-0.8)	0.7
Platelet count (10^3/mm³)	126 (118-136)	122 (110-133)	136 (123-155)	0.1	125 (108-145)	126 (116-140)	0.8
Child-Pugh score*	5 (5-5)	5 (5-5)	5 (5-5)	0.4	5 (5-5)	5 (5-5)	0.2
MELD score*	8.1 (7.6-8.6)******	8.5 (7.6-9.1)	7.8 (7.4-8.2)	0.055	8.1 (7.4-8.7)	8.0 (7.6-8.8)	0.3
Alcohol consumption during follow-up (No. of consumers, %)	74 (38%)	0 (0%)	74 (100%)	<0.001	24 (35%)	50 (40%)	0.5
Alcohol consumption during follow-up (g/day)*	0 (0-0)	0 (0-0)	15 (5-20)	<0.001	0 (0-0)	0 (0-0)	0.3
Antiviral treatment (No. of patients treated, %)	166 (86%)	97 (82%)	69 (93%)	0.03	68 (100%)	98 (79%)	<0.001
Viral eradication (No. of patients with viral eradication, %)	68 (35%)	44 (37%)	24 (32%)	0.5	68 (100%)	0 (0%)	<0.001

BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; MELD, model for end-stage liver disease.
*Data expressed as median (95% CI). **Data available in 188 patients. ***Data available in 191 patients. ****Data available in 186 patients. *****Data available in 175 patients. ******Data available in 177 patients.

Table 2. Clinical events according to alcohol consumption and viral eradication.

Characteristics	Overall (n = 192)	Abstainers (n = 118)	Consumers (n = 74)	*p* value	With viral eradication (n = 68)	Without viral eradication (n = 124)	*p* value
HCC (No., %)	33 (17%)	16 (14%)	17 (23%)	0.09	7 (10%)	26 (21%)	0.06
Decompensation of cirrhosis (No., %)	53 (28%)	32 (27%)	21 (28%)	0.8	10 (15%)	43 (35%)	0.003
Overall deaths (No., %)	39 (20%)	24 (20%)	15 (20%)	1.0	2 (3%)	37 (30%)	<0.001
Liver-related deaths (No., % of deaths)	28 (77%)	16 (78%)	12 (80%)	0.6	1 (50%)	27 (73%)	<0.001
Decompensation-related deaths (No., % of deaths)	19 (53%)	12 (50%)	7 (47%)		0 (0%)	19 (51%)	
HCC-related deaths (No., % of deaths)	9 (23%)	4 (17%)	5 (33%)		1 (50%)	8 (22%)	
Non-liver-related deaths (No., % of deaths)	11 (23%)	8 (33%)	3 (20%)	0.4	1 (50%)	10 (27%)	0.06
Liver transplantation (No., %)	20 (10%)	12 (10%)	8 (11%)	0.9	7 (10%)	13 (10%)	1.0

HCC, hepatocellular carcinoma.

2 out of 68 patients with viral eradication (3%) and 37 out of 124 patients without viral eradication (30%) died (p <0.001). Among patients with viral eradication, cause of death was HCC in 1 case (50%) and non-liver-related in 1 case (50%). Among patients without viral eradication, cause of death was HCC in 8 cases (22%), decompensation of cirrhosis in 19 cases (51%), and non-liver-related in 10 cases (27%).

Cumulative incidence of HCC and factors predicting HCC

The 5-year cumulative incidence rate of HCC was 10.6% (95% CI: 4.6–16.6) in abstainers and 23.8% (95% CI: 13.5–34.1) in alcohol consumers (p = 0.087) (Fig. 1A). Average annual HCC rates were 2.3% (95% CI: 0.1–4.7) and 5.9% (95% CI: 2.3–8.1) in abstainers and consumers, respectively. The 5-year cumulative incidence rate of HCC was 2.0% (95% CI: 0–5.8) in patients with viral eradication and 21.7% (95% CI: 14.2–29.2) in patients without viral eradication (p = 0.002) (Fig. 1B). Average annual HCC rates were 0.4% (95% CI: 0–1.8) and 5.4% (95% CI: 1.5–8.6) in patients with and without viral eradication, respectively. In time-dependent multivariate proportional hazards models, lack of viral eradication and alcohol consumption were associated with an increased risk of HCC (Table 3). Tobacco use was not associated with an increased risk of HCC.

The 5-year cumulative incidence rate of HCC according to alcohol intake and viral eradication is given in Supplementary Table 2.

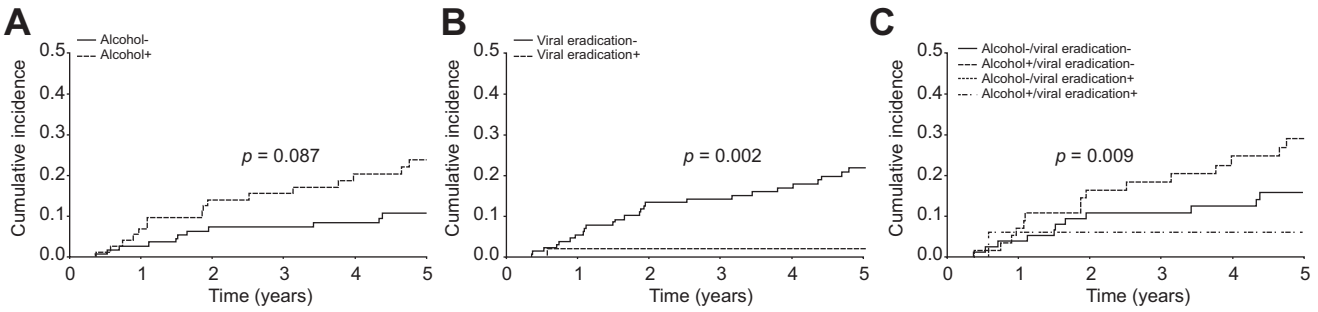

Fig. 1. 5-year cumulative incidence rate of HCC. (A) 5-year cumulative incidence rate of HCC according to alcohol intake. (B) 5-year cumulative incidence rate of HCC according to viral eradication. (C) 5-year cumulative incidence rate of HCC according to alcohol intake and viral eradication. HCC, hepatocellular carcinoma.

Table 3. Risk factors for the development of HCC or decompensation of cirrhosis.

		HCC				Decompensation			
		Univariate		Multivariate		Univariate		Multivariate	
Baseline characteristics	Comparison group	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age	1-year increase	1.03 (1.00-1.06)	0.03	1.06 (1.02-1.09)	<0.001	0.98 (0.96-1.00)	0.12		
Sex	Male *vs.* female	0.57 (0.27-1.23)	0.15			0.97 (0.54-1.74)	0.9		
Diabetes	Yes *vs.* no	1.21 (0.59-2.51)	0.6			0.86 (0.46-1.60)	0.6		
BMI	1-point increase	1.00 (0.91-1.09)	0.9			1.03 (0.96-1.12)	0.4		
Past alcohol intake	Yes *vs.* no	0.82 (0.41-1.63)	0.6			1.32 (0.71-2.45)	0.4		
Tobacco use	Yes *vs.* no	1.17 (0.54-2.54)	0.7			1.54 (0.83-2.85)	0.2		
Child-Pugh score	1-point increase	0.91 (0.30-2.73)	0.9			2.59 (1.31-5.09)	0.006	1.38 (0.62-3.06)	0.4
MELD score	1-point increase	1.05 (1.03-1.07)	<0.001	1.02 (0.99-1.04)	0.2	1.05 (1.03-1.08)	<0.001	1.02 (0.99-1.04)	0.2
Platelet count	10^3/mm^3 increase	0.99 (0.99-1.00)	0.06	0.99 (0.99-1.00)	0.065	0.99 (0.98-0.99)	<0.001	0.99 (0.99-1.00)	0.02
Alcohol intake during follow-up	Yes *vs.* no	1.84 (0.92-3.67)	0.08	3.43 (1.49-7.92)	0.004	1.22 (0.69-2.16)	0.5		
Alcohol intake during follow-up	1-g/day increase	1.00 (0.99-1.01)	0.6			1.01 (1.00-1.02)	0.01	1.01 (1.00-1.01)	0.12
Antiviral treatment	Yes *vs.* no	1.75 (0.41-7.56)	0.4			0.79 (0.33-1.87)	0.6		
Viral eradication	Yes *vs.* no	0.15 (0.04-0.64)	0.01	0.12 (0.02-0.90)	0.04	0.09 (0.02-0.37)	<0.001	0.12 (0.03-0.51)	0.004

BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

The lowest risk was observed for patients without alcohol intake and with viral eradication (0%) followed by patients with alcohol intake and viral eradication (6.2% [95% CI: 0–18.4]), patients without alcohol intake and no viral eradication (15.9% [95% CI: 7.1–24.7]), and patients with alcohol intake and no viral eradication (29.2% [95% CI: 16.5–41.9]) ($p = 0.009$) (Fig. 1C).

Cumulative incidence of decompensation of cirrhosis and factors predicting decompensation

The 5-year cumulative incidence rate of decompensation of cirrhosis was 18.4% (95% CI: 10.8–26.0) in abstainers and 22.3% (95% CI: 12.2–32.4) in consumers ($p = 0.6$) (Fig. 2A). Average annual rates of decompensation of cirrhosis were 4.1% (95% CI: 1.6–6.8) and 5.7% (95% CI: 4.7–7.5) in abstainers and consumers, respectively. The 5-year cumulative incidence rate of decompensation of cirrhosis was 4.0% (95% CI: 0–9.5) in patients with viral eradication and 26.6% (95% CI: 18.6–34.6) in patients without viral eradication ($p = 0.001$) (Fig. 2B). Average annual rates of decompensation of cirrhosis were 0.8% (95% CI: 0–2.1) and 6.7% (95% CI: 5.0–9.6) in patients with and without viral eradication, respectively. Results of time-dependent multivariate proportional

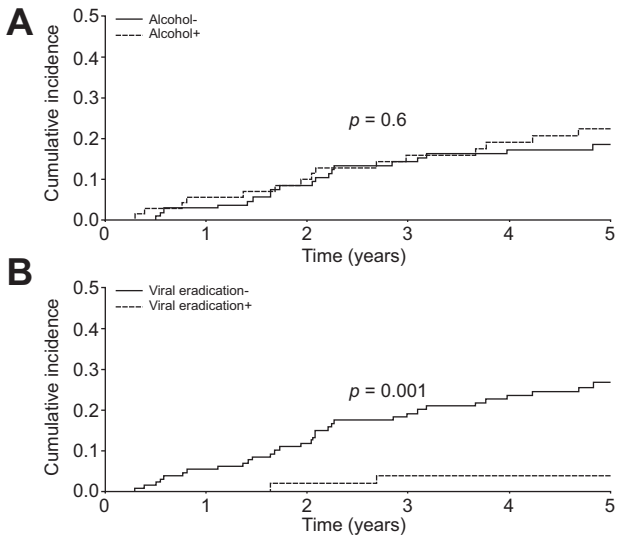

Fig. 2. 5-year cumulative incidence rate of decompensation. (A) 5-year cumulative incidence rate of decompensation according to alcohol intake. (B) 5-year cumulative incidence rate of decompensation according to viral eradication.

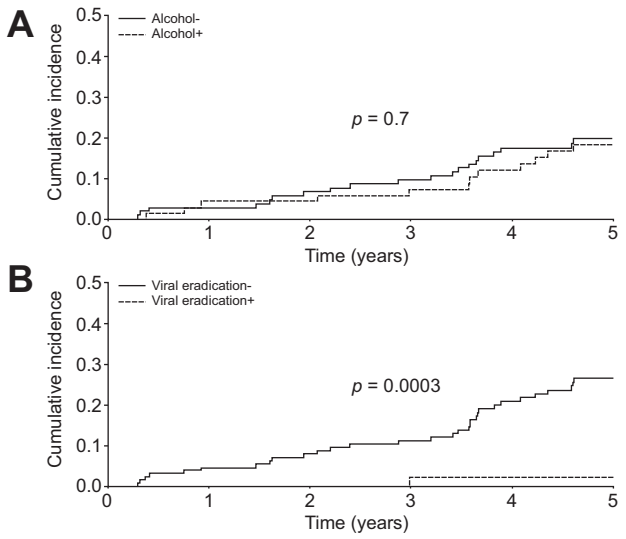

Fig. 3. 5-year cumulative incidence rate of mortality. (A) 5-year cumulative incidence rate of mortality according to alcohol intake. (B) 5-year cumulative incidence rate of mortality according to viral eradication.

hazards models for predicting decompensation of cirrhosis are reported in Table 3. Viral eradication was associated with a reduced risk of decompensation of cirrhosis.

The 5-year cumulative incidence rate of decompensation of cirrhosis according to alcohol intake and viral eradication is given in Supplementary Table 2. The lowest risk was observed for patients without alcohol intake and with viral eradication (2.9% [95% CI: 0–8.7]) compared to other patients ($p = 0.012$).

Five-year mortality, liver-related mortality and factors predicting death

The 5-year cumulative incidence rate of mortality was 19.6% (95% CI: 11.8–27.4) in abstainers and 18.2% (95% CI: 8.7–27.7) in consumers ($p = 0.7$) (Fig. 3A). Average annual mortality rates were 4.4% (95% CI: 2.6–8.9) and 4.1% (95% CI: 0.3–7.7) in abstainers and consumers, respectively. The 5-year cumulative incidence rate of liver-related mortality was 13.6% (95% CI: 6.9–20.3) in abstainers and 13.9% (95% CI: 5.4–22.4) in consumers ($p = 0.8$). Average annual liver-related mortality rates were 3.0% (95% CI: 1.4–5.7) and 3.1% (95% CI: 0.2–7.6) in abstainers and consumers, respectively. The 5-year cumulative incidence rate of mortality was 2.0% (95% CI: 0–5.9) in patients with viral eradication and 26.1% (95% CI: 18.1–34.1) in patients without viral eradication ($p < 0.001$) (Fig. 3B). Average annual mortality rates were 0.4% (95% CI: 0–1.8) and 6.2% (95% CI: 3.3–11.3) in patients with and without viral eradication, respectively. The 5-year cumulative incidence rate of liver-related mortality was 2.0 (95% CI: 0–5.9) in patients with viral eradication and 18.6% (95% CI: 11.5–25.7) in patients without viral eradication ($p = 0.002$). Average annual liver-related mortality rates were 0.4% (95% CI: 0–1.8) and 4.4% (95% CI: 2.0–7.4) in patients with and without viral eradication, respectively. Results of time-dependent multivariate proportional hazards models for predicting all-cause mortality and liver-related mortality are reported in Table 4. Viral eradication was associated with reduced all-cause mortality and liver-related mortality.

The 5-year cumulative incidence rates of mortality and liver-related mortality according to alcohol intake and viral eradication are given in Supplementary Table 3. Compared to other patients, those without alcohol intake and with viral eradication had the lowest risk of death (0%, $p = 0.002$) and the lowest risk of liver-related death (0%, $p = 0.016$).

Discussion

The main goal of this study was to prospectively assess the impact of alcohol intake and viral eradication on the risk of HCC, decompensation of cirrhosis and death in patients with compensated HCV-related cirrhosis. To the best of our

Table 4. Risk factors for overall mortality and for liver-related mortality.

		Mortality				Liver-related mortality			
		Univariate		Multivariate		Univariate		Multivariate	
Baseline characteristics	Comparison group	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age	1-year increase	1.03 (1.00-1.06)	0.04	1.01 (0.99-1.04)	0.3	1.01 (0.98-1.05)	0.4		
Sex	Male *vs.* female	1.60 (0.86-2.98)	0.14			1.04 (0.48-2.22)	0.9		
Diabetes	Yes *vs.* no	1.30 (0.68-2.47)	0.4			0.90 (0.40-2.02)	0.8		
BMI	1-point increase	1.07 (1.00-1.15)	0.05	1.07 (0.99-1.16)	0.07	1.10 (1.02-1.18)	0.01	1.06 (0.96-1.17)	0.3
Past alcohol intake	Yes *vs.* no	1.71 (0.83-3.53)	0.15			1.18 (0.52-2.63)	0.7		
Tobacco use	Yes *vs.* no	1.39 (0.71-2.75)	0.3			2.26 (1.03-4.94)	0.04	2.45 (1.01-5.95)	0.048
Child-Pugh score	1-point increase	1.72 (0.80-2.72)	0.17			1.40 (0.53-3.69)	0.5		
MELD score	1-point increase	1.05 (1.03-1.07)	<0.001	1.04 (1.02-1.06)	<0.001	1.06 (1.04-1.07)	<0.001	1.02 (0.99-1.04)	0.2
Platelet count	10^3/mm^3 increase	1.00 (0.99-1.00)	0.7			0.99 (0.99-1.00)	0.06	1.00 (0.99-1.00)	0.2
Alcohol intake during follow-up	Yes *vs.* no	0.90 (0.48-1.70)	0.7			1.10 (0.53-2.28)	0.8		
Alcohol intake during follow-up	1-g/day increase	0.99 (0.98-1.01)	0.4			1.00 (0.99-1.01)	0.9		
Antiviral treatment	Yes *vs.* no	0.28 (0.14-0.59)	<0.001	0.51 (0.21-1.26)	0.14	0.45 (0.17-1.19)	0.11		
Viral eradication	Yes *vs.* no	0.10 (0.02-0.41)	0.001	0.15 (0.04-0.59)	0.007	0.07 (0.01-0.55)	0.01	0.10 (0.01-0.79)	0.03

BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

knowledge, this question has not been previously addressed prospectively. Three main conclusions can be drawn.

Firstly, alcohol intake was associated with an increased risk of HCC. As the median amount of alcohol intake was low in consumers (15 g/day, 95% CI: 5–20), we can conclude that light-to-moderate alcohol intake increases the risk of HCC in HCV patients with compensated cirrhosis. In addition, the amount of alcohol intake did not impact the risk of HCC, suggesting that there is no safe threshold for alcohol in these patients. This is a major finding as alcohol use and HCV infection frequently coexist [30]. Daily intake of small amounts of alcohol is usually considered non-detrimental to general health or to the liver, and sometimes is even considered beneficial. Several studies have shown that the mortality rate in the general population is increased in people who never drink alcohol compared to people who drink less than 20 g per day [31]. The results of the present study contrast with these concepts and with the results of the first report of the CirVir prospective cohort study that has been recently published [32]. In this study, alcohol intake was recorded only at inclusion and not during follow-up, and the follow-up period was very short, which may explain why alcohol intake was not found to be associated with the development of HCC. The mechanisms through which alcohol increases the risk of HCC are not fully understood. Several lines of evidence indicate that chronic alcohol use leads to multiple biochemical changes that could increase the risk of HCC [33]. Experimentally, moderate alcohol intake may promote oxidative stress in HCV patients that may favor the development of HCC [34]. In addition, acetaldehyde, a key metabolite of ethanol, is considered a carcinogen that may alter DNA repair [35]. Of note, tobacco use, a recognized risk factor for the development of many tumors, was not associated with an increased risk of HCC, nor was BMI.

The second key finding of this study is the increase in the risk of HCC according to alcohol intake and to the lack of viral eradication. Since SVR is a durable event irrespective of the treatment type, novel interferon-free regimens should not outdate these findings, even if interferon-based therapies may combine antiviral and antiproliferative properties. The lowest risk of HCC was observed in patients who did not use alcohol and who reached viral eradication. None of these patients developed HCC during follow-up. The risk increased with alcohol intake or in patients without viral eradication and was highest when alcohol intake was present in the absence of viral eradication. Thus, the risk of HCC was not completely abolished in patients who reached SVR which was expected since cirrhosis in itself is a major independent risk factor for HCC [21,22].

The last conclusion of this study is that alcohol intake did not influence the risk of decompensation of cirrhosis or the risk of death. However, for these analyses, higher alcohol intake and/or larger amount of data may be required. Evidence obtained mainly from cross-sectional studies show that alcohol abuse is associated with liver fibrosis and liver cirrhosis in HCV patients, which results in higher liver-related deaths [5,6,13,36]. On the other hand, viral eradication was associated with reduced mortality and liver-related mortality, which is consistent with the results of previous studies showing that curing HCV infection results in reduced mortality rates [17,23,37,38]. Unfortunately, our study was not powered to identify which patients with viral eradication will develop liver-related complications or die. Another point of interest concerns non-liver-related deaths. Most of these deaths were due to cardiovascular events. Overall, non-liver-related deaths accounted for 28% of all deaths, which is lower than in a recent prospective study [32]. One possible explanation could be that, in the latter study, deaths due to bacterial infection were considered as non-liver-related whereas they were considered as liver-related in our study when they resulted in liver failure. Non-liver-related deaths were as frequent in abstainers as in alcohol consumers, but numerically lower in patients with viral eradication than in those without. All but one non-liver-related death occurred in patients without viral eradication. These results indirectly suggest that viral eradication could also protect against non-liver-related morbidity, as already shown by others [23].

This study has several limitations. Firstly, in cohort studies with no control group, prognostic factors other than alcohol intake or viral eradication might hamper the validity of the results. However, patients were recruited in the same country, during the same period using the same strict criteria. Thus, they were likely to have been exposed to similar risk factors. One feature that was only partially taken into account was the individual susceptibility of HCV patients to the effects of alcohol [39]. It is well accepted that alcoholic liver disease in the absence of HCV develops only in a subset of drinkers. It is likely that such susceptibility also plays a role in patients with chronic HCV infection. Another weakness is the assessment of alcohol consumption according to patient declarations and not through the use of a standard questionnaire. In addition, a liver biopsy was not systematically performed. This point must be acknowledged in consumers in whom alcohol intake could have increased liver stiffness. However, apart from a younger age and a higher access to antiviral therapy, patients for whom the diagnosis of cirrhosis was made with a liver biopsy had similar characteristics to those for whom the diagnosis of cirrhosis was made without a liver biopsy. Finally, the sample size was limited. Conversely, our study presents robust advantages. In addition to the strict selection of patients, the prospective design of the study enabled us to be confident with the results. The annual rates of HCC and decompensation of cirrhosis were 3.6% and 4.7%, respectively, which is similar to those found in previous reports [3,4,40,41]. In addition, detailed analysis of the causes of death was performed, enabling us to study all causes of mortality as a single outcome as well as liver-related mortality using cumulative incidence functions, as recommended [28].

In conclusion, light-to-moderate alcohol intake increases the risk of HCC in patients with HCV-related cirrhosis. There is an increase in the risk of HCC according to alcohol intake and the lack of viral eradication. Accordingly, patients with HCV-related cirrhosis should be strongly advised against any alcohol intake. Patient care should include measures to ensure abstinence.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

Hélène Vandenbulcke: acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the

manuscript for important intellectual content; Christophe Moreno: acquisition of data; critical revision of the manuscript for important intellectual content; Isabelle Colle: acquisition of data; critical revision of the manuscript for important intellectual content; Jean-François Knebel: statistical analysis; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; Sven Francque: acquisition of data; critical revision of the manuscript for important intellectual content; Thomas Sersté: acquisition of data; critical revision of the manuscript for important intellectual content; Christophe George: acquisition of data; critical revision of the manuscript for important intellectual content; Chantal de Galocsy: acquisition of data; critical revision of the manuscript for important intellectual content; Wim Laleman: acquisition of data; critical revision of the manuscript for important intellectual content; Jean Delwaide: acquisition of data; critical revision of the manuscript for important intellectual content; Hans Orlent: acquisition of data; critical revision of the manuscript for important intellectual content; Luc Lasser: acquisition of data; critical revision of the manuscript for important intellectual content; Marie de Vos: acquisition of data; critical revision of the manuscript for important intellectual content; Eric Trépo: acquisition of data; critical revision of the manuscript for important intellectual content; Hans Van Vlierberghe: acquisition of data; critical revision of the manuscript for important intellectual content; Peter Michielsen: acquisition of data; critical revision of the manuscript for important intellectual content; Marc van Gossum: acquisition of data; critical revision of the manuscript for important intellectual content; Astrid Marot: critical revision of the manuscript for important intellectual content; Christopher Doerig: critical revision of the manuscript for important intellectual content; Jean Henrion: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; Pierre Deltenre: study concept and design; acquisition of data; statistical analysis; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2016.04.031.

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