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PNPLA3, obesity and heavy alcohol use in cirrhosis patients may exert a synergistic increase hepatocellular carcinoma risk

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Abstract

Background & Aims: In patients with cirrhosis, continued heavy alcohol consumption and obesity may increase risk of hepatocellular carcinoma (HCC). We examined whether germline susceptibility to hepatic steatosis not only independently predisposes to HCC but may also act synergistically with other risk factors.

Methods: We analyzed data from 1911 patients in two multicenter prospective cohort studies in the U.S. We classified patients according to alcohol consumption (current heavy vs. not current heavy), obesity (body mass index [BMI] ≥30 vs. <30), and *PNPLA3* I148M variant status (carrier of at least one G risk allele vs. noncarrier). We examined the independent and joint effects of these risk factors on risk of developing HCC using Cox regression with competing risks.

Results: Mean age was 59.6y, 64.3% male, 28.7% Hispanic, 18.3% non-Hispanic Black, 50.9% were obese, 6.2% had current heavy alcohol consumption, and 58.4% harbored at least one *PNPLA3* G-allele. 116 patients developed HCC. Compared to *PNPLA3* noncarriers without heavy alcohol consumption, HCC risk was 2.65-fold higher (hazard ratio [HR], 2.65; 95% confidence

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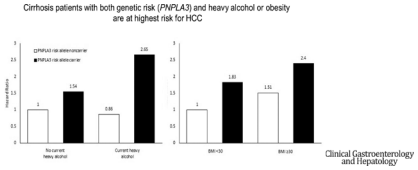
interval [CI], 1.20–5.86) for carriers who had current heavy alcohol consumption. Compared to noncarrier patients without obesity, HCC risk was higher (HR, 2.40; 95%CI, 1.33–4.31) for carrier patients who were obese. *PNPLA3* and alcohol consumption effect was stronger among patients with viral etiology of cirrhosis (HR, 3.42; 95% CI, 1.31–8.90). *PNPLA3* improved 1-year risk prediction for HCC when added to a clinical risk model.

Conclusions: The *PNPLA3* variant may help refine risk stratification for HCC in patients with cirrhosis with heavy alcohol consumption or obesity who may need specific preventive measures.

Graphical Abstract



INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of death worldwide.[1] In the United States, HCC incidence and mortality have increased rapidly over the past three decades.[2,3] Cure is only possible for fewer than 10% of HCC patients whose cancer is detected early and who receive liver transplantation or surgical resection.[4] Most HCC patients are diagnosed with advanced disease. As a result, the overall 5-year survival rate for HCC patients in the U.S. remains less than 20%.[4]

Adiposity and heavy alcohol consumption are important contemporary risk factors for HCC.[5,6] Individuals with a body mass index (BMI) of 30 kg/m^2 or more have 2-fold increased risk of developing HCC,[7] with early adulthood weight gain associated with higher risk.[8] Likewise, compared to non-drinkers, individuals consuming ≥7 alcoholic drinks/day on average have 2-fold increased HCC risk.[6] Studies in the general population have shown that alcohol and obesity synergistically (i.e., the joint effect is greater than the sum of their separate effects) increase the risk of HCC.[9] Similarly,[10] high BMI and alcohol consumption were both independently as well as synergistically associated with increased risk of liver disease morbidity and mortality in the general population of Scotland. Genetic factors may help to identify patients at highest risk of progression to HCC. In particular, the rs738409 C>G single-nucleotide variant (I148M) in the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene is a key player in development and progression of fatty liver.[11–13] Furthermore, in our recent analysis among participants in the UK Biobank, we found synergistic associations between the *PNPLA3* I148M variant, excessive alcohol consumption, and obesity with increased risks of liver disease morbidity and mortality.[14] HCC risk and liver-disease related mortality was 20–30-fold higher among individuals in the UK general population with these 3 risk factors compared to individuals without any of these factors.[14]

Preventive efforts and early detection through screening and subsequent surveillance, and possibly chemoprevention are necessary for reducing HCC-related mortality in patients with cirrhosis.[4] Although cirrhosis is the main precursor lesion in HCC, most patients with

cirrhosis do not progress to HCC, and therefore most of the preventive efforts would be misplaced if applied to all patients with cirrhosis. There is a knowledge gap about risk stratification from actionable risk factors for HCC among patients with cirrhosis. None of the studies of the 3 risk factors (*PNPLA3*, alcohol and obesity) were conducted among patients with cirrhosis. In the current study, we aimed to investigate the joint associations of the *PNPLA3* I148M variant, alcohol intake, and obesity with the risk of progression to HCC in a contemporary cohort of patients with cirrhosis. We hypothesized that, in addition to independently predisposing patients with cirrhosis to HCC, the *PNPLA3* I148M variant would act synergistically with alcohol intake and obesity to increase HCC risk in patients with cirrhosis. If found to be true, these findings could inform risk stratification in cirrhosis.

METHODS

Study Population

We used data from patients recruited and enrolled into the Texas Hepatocellular Carcinoma Consortium Cohort (THCCC) and the Houston Veterans Administration Cirrhosis Surveillance Cohort (HVASC) studies.[11,15,16] This study was approved by the Institutional Review Board at Baylor College of Medicine. All participants provided written informed consent to participate.

The THCCC is an ongoing study that prospectively recruits patients with cirrhosis from seven institutions in four cities in Texas.[17] For the current analysis, we included THCCC participants enrolled between December 2016 and April 2020, with follow-up until December 31, 2022. Cirrhosis diagnosis was based on predefined criteria for liver histology, radiology, liver elastography, or serum biomarkers.[16] We excluded patients with uncontrolled hepatic decompensation, history of HCC, or presence of non-hepatic cancer at baseline. Patients completed surveys including medical history and alcohol and tobacco use. We also abstracted data from the patients' electronic medical records (EMRs) including (1) clinician-recorded diagnoses including cirrhosis etiology (e.g., HCV or hepatitis B virus [HBV] infection), complications of liver disease (ascites, varices, encephalopathy); (2) liver imaging and biopsy results; and (3) laboratory data within 12 months of enrollment. Patients were scheduled for 6-month visits as part of routine clinical care and followed until HCC diagnosis, liver transplantation, or death. They received ultrasound, CT, or MRI for HCC surveillance per the decision of treating physician. All patients had baseline imaging as this was a criterion to be included in the cohort. Approximately 80% of our cohort underwent at least one additional HCC surveillance test mostly ultrasound.

HVASC is a cohort of patients with cirrhosis in active HCC surveillance recruited from hepatology clinics at the Michael E. DeBakey VA Medical Center between August 2014 and December 2016. Like THCCC, HVASC patients were followed for outcomes (HCC) until December 31, 2022. HVASC used similar inclusion and exclusion criteria and recruitment procedures as those described for THCCC. Data from THCCC and HVASC were harmonized into a common dataset using the steps described by Rolland et al.[18]

Outcome

Our primary outcome was the development of HCC any time after enrollment. HCC was defined according to histological or radiological diagnosis using characteristic appearance (arterial enhancement and delayed washout) on triple-phase CT or MRI (Liver Imaging Reporting and Data System [LI-RADS] 5) or those with LI-RADS 4 lesions that were reviewed in multidisciplinary tumor boards and treated as HCC and adjudicated centrally. EMR reviews were conducted for all participants at 3-month intervals to capture incident HCCs, liver transplantation, and death dates. All study sites have multidisciplinary HCC tumor boards, and, for the current analysis, the date of final confirmation was used as the date of HCC diagnosis.[17]

Obesity and Alcohol Consumption

Obesity was defined as BMI ≥30 kg/m^2, which was calculated using height and weight values at enrolment in the cohort. We used a survey to ascertain alcohol use that classified alcohol use status as lifetime abstention (never), former light to moderate use, former heavy use, current light to moderate use, and current heavy use. For the primary analysis, we compared patients with cirrhosis with current heavy alcohol use to those without current heavy alcohol use. We considered current heavy alcohol use as self-reported current (time of study recruitment) consumption of 8 or more alcoholic drinks per week for women or 15 or more alcoholic drinks per week for men.

Genotyping of the *PNPLA3* I148M Variant

The *PNPLA3* I148M variant was genotyped using the Affymetrix Axiom Precision Medicine Research Array.[11] This information was coded as 0 for noncarriers (CC genotype), 1 for heterozygous carriers (GC genotype), and 2 for homozygous carriers (GG genotype) of the minor allele (G allele). For the primary analysis, we compared noncarriers with carriers (GC or GG genotype).

Covariables

We recorded patient's age at enrollment, sex, and self-reported race and ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, and other groups). Etiology of cirrhosis was active HCV if the patient had a positive HCV RNA test, and cured HCV if there was sustained virological response (SVR) at the time of enrollment;[19] HBV was based on a positive HBsAg;[20,21] and alcohol-related cirrhosis based on a clinician-recorded diagnosis of alcohol-related liver disease and patients' self-report of former heavy (8 or more alcoholic beverages per week for women or 15 or more alcoholic beverages per week for men) or any current use of alcohol. The diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD) required documentation of hepatic steatosis on liver histology or imaging and the absence of HCV (active/untreated or resolved HCV), HBV, alcohol-related liver disease, or other clinician documented etiologies.[22] Most (>90%) patients classified as MASLD also had a clinician-recorded diagnosis of MASLD in the EMR. We defined diabetes, hypertension, and dyslipidemia based on patients' medical history (survey or EMR) or self-reported treatment with diabetes medications, antihypertensives, or treatments

for dyslipidemia at any time before enrollment. We defined smoking status as never, past, and current smokers based on self-report using the baseline survey.

Statistical Analysis

Patients with cirrhosis were followed from the date of enrollment in THCCC/HVASC to the development of HCC, death, liver transplantation, or end of follow-up (i.e., last study visit). We estimated hazard ratios (HR) and 95% confidence intervals (95% CI) for associations with incident HCC risk using Fine-Gray competing risk regression models, that accounted for the competing risk of death. First, we examined whether *PNPLA3* I148M variant, obesity, and alcohol consumption were independently associated with HCC risk after adjusting for potential confounders including age, sex, race/ethnicity, and HCV status. We then estimated the adjusted hazard of HCC risk between individuals with different combinations of risk factors (e.g., no current heavy alcohol use and noncarrier of the *PNPLA3* I148M variant; no current heavy alcohol use and carrier of the *PNPLA3* I148M variant; current heavy alcohol use and noncarrier of the *PNPLA3* I148M variant; and current heavy alcohol use and carrier of the *PNPLA3* I148M variant). We also performed these analyses in subgroups defined by cirrhosis etiology and by race/ethnicity to examine for potential differences in the associations with the HCC. In a sensitivity analysis, we re-examined associations after excluding patients who were diagnosed with HCC during the first 3 months of follow-up. In an exploratory analysis, we also examined synergistic interaction between the 3 factors. Finally, we examined whether *PNPLA3* can be used to improve risk prediction for HCC in cirrhosis patients. We computed the integrated discrimination improvement (IDI) and net reclassification index (NRI) using the cause-specific model to assess the impact of adding the genetic variable (*PNPLA3*) to our previously developed and validated base model including terms for age, gender, AFP, platelets, ALT, albumin, BMI, smoking, alcohol, and HCV status.[23,24] IDI is used to evaluate the overall improvement of the model, while NRI refers to the difference in the proportion of patients with a higher probability of events being correctly assigned and a lower probability of events being correctly assigned in the updated model compared to the original model.[25] Analyses were conducted using SAS version 9.4 and R.

RESULTS

We analyzed data from 1,911 patients with cirrhosis (Table 1). The mean age of patients was 59.6 years (standard deviation, 10.0); and 35.7% were female. The racial and ethnic distribution was 50.4% non-Hispanic White, 28.7% Hispanics, 18.3% non-Hispanic Black, and 2.6% belonging to other racial groups. Cirrhosis etiology was active HCV in 255 (13.3%), cured HCV in 513 (26.8%), MASLD in 591 (30.9%), ALD in 320 (16.8%), and other etiologies in 232 (12.1%) patients. Among the cohort, 50.9% were obese, 31.6% overweight, 6.2% had current heavy alcohol consumption (62.6% past or current non-heavy drinkers), and 58.4% harbored at least one *PNPLA3* G-allele (i.e., heterozygous carriers) and 20.4% were homozygous carriers. During 6,692 person-years of follow-up, 116 patients developed incident HCC (annual incidence rate, 1.73%; 95% CI, 1.44–2.08). The mean duration between enrollment and HCC development was 2.21 (± 1.45) years. The

cumulative incidence of HCC varied by sex, race/ethnicity, obesity status, alcohol use and PNPLA3 status (Supplementary Table 1).

In the multivariable model that adjusted for age, sex, race/ethnicity and HCV status, *PNPLA3* carrier status was statistically significantly associated with HCC risk (Table 2). Compared to noncarriers, patients with at least one risk allele (*PNPLA3* carriers) had a 1.62-fold higher risk of progressing to HCC (HR, 1.62; 95% CI, 1.08–2.45; p=0.02). Patients with current heavy alcohol consumption or obesity had a 1.43-fold and 1.37-folder higher risk of HCC, respectively, although these associations did not reach statistical significance (p=0.28 and 0.10, respectively). These associations were similar when examined separately for males and females (Supplementary Table 2). However, there were too few current heavy drinkers among females to examine the association of heavy alcohol use with HCC risk.

We found evidence for potential synergistic interactions between the *PNPLA3* I148M variant and each of alcohol consumption and BMI. Compared to noncarrier patients without current heavy alcohol consumption, risk of HCC was 2.65-fold higher (HR, 2.65; 95%CI, 1.20–5.86; p=0.02) for carrier patients who had current heavy alcohol consumption (Table 3). Heavy alcohol consumption without additional genetic effect did not confer increased HCC risk. Noncarrier cirrhosis patients with current heavy alcohol consumption had no increased risk of HCC compared to noncarrier patients without current heavy alcohol consumption (HR, 0.86; 95%CI, 0.21–3.54; p=0.84). The synergistic association between *PNPLA3* and alcohol consumption was stronger among patients with viral etiology HR, 3.42; 95% CI, 1.31–8.90) than in patients with cirrhosis without viral hepatitis etiology (HR, 1.87; 95% CI, 0.39–9.07) (Supplementary Table 3). There was no evidence of synergism between *PNPLA3* and alcohol consumption in analyses limited to non-Hispanic white patients with cirrhosis (Supplementary Table 4).

There was also evidence for synergistic interaction between *PNPLA3* and obesity on HCC risk. Compared to noncarrier patients without obesity, risk of HCC was higher (HR, 2.40; 95%CI, 1.33–4.31; p=0.004) for carrier patients with obesity. Among non-obese patients, carriers had 1.83-fold higher risk (95% CI, 1.01–3.35; p=0.05) for HCC than noncarriers (Table 3). We found no clear associations between the combined exposure to both *PNPLA3* and obesity on HCC risk in analyses stratified by etiology (Supplementary Table 3). However, among NHW patients with cirrhosis, carrier patients with obesity had almost 3-fold significantly higher HCC risk (Supplementary Table 4). There was no synergistic association between obesity and heavy alcohol consumption on risk of HCC in patients with cirrhosis after adjusting for *PNPLA3* (Table 3).

Similar associations were observed in a sensitivity analysis in which we excluded 5 patients with HCC diagnosed within the first 3 months of follow-up (Supplementary Table 5).

In an exploratory analysis that examined combinations of the 3 risk factors, carriers with current heavy alcohol consumption had highest rates of progression to HCC regardless of obesity status (Figure 1). However, patients who had current heavy alcohol consumption and were obese also had high rates of HCC irrespective of carrier status, suggesting no additional synergistic genetic effect (Supplementary Table 6). The absence of all 3 risk factors had a

very high negative predictive value (95.5%−96.0%) for HCC (Supplementary Table 7), but the annual incidence of HCC was still high 1.23% (95% CI, 0.78–1.95).

Adding *PNPLA3* to the base HCC risk predictive model increased the c-index for predicting 1-year risk for HCC from 0.78 (95% CI, 0.66–0.90) to 0.83 (95% CI, 0.72–0.94) but not the 2-year risk for HCC (base model, 0.74; 95% CI, 0.66–0.81; *PNPLA3* added, 0.75; 95% CI, 0.68–0.83). Similarly, the calculation results of IDI and NRI confirmed that adding *PNPLA3* improved the risk reclassification for 1-year HCC risk (IDI, 0.004, p=0.01; NRI, 0.30, p=0.02) but not 2-year HCC risk (IDI, 0.003, p=0.19; NRI, 0.15, p=0.04).

DISCUSSION

In this longitudinal prospective cohort study of patients with cirrhosis, we examined whether the *PNPLA3* I148M variant acts synergistically with alcohol intake and/or obesity to influence an individual's risk for HCC. Our study had four major findings. First, we found that carriers of the *PNPLA3* G risk allele had 1.6-fold higher risk of HCC compared to noncarriers. Second, we found synergistic associations of *PNPLA3* with each of heavy alcohol consumption and obesity. Patients with cirrhosis who were carriers of the *PNPLA3* risk allele and had either a history of heavy alcohol consumption or obesity had excess risk of progression to HCC. Third, the existence and magnitude of this synergistic association varied by cirrhosis etiology and by race/ethnicity. This likely reflects the differences in the underlying mechanisms that lead to cirrhosis in different subgroups of patients with cirrhosis. Fourth, *PNPLA3* may improve short-term risk prediction for HCC among patients with cirrhosis when added to a previously validated predictive model that contained clinical and demographic variables.

Our results have several important implications. Genotyping for the *PNPLA3* I148M variant may also be useful in refining the risk stratification of patients with cirrhosis. Consistent with prior studies,[11] we showed that adding *PNPLA3* provided some improvement in risk prediction for HCC over that of our previously validated model.[23,24] However, additional factors are likely needed to enhance clinical utility of risk stratification models, especially to inform which patients can be safely discharged from HCC surveillance.[11] Furthermore, due to differences in allele frequency among patients of different genetic ancestry, ancestry-specific analyses and risk models developed among individuals of similar ancestry may be necessary for an optimized risk stratification. Last, these 3 factors -- *PNPLA3* I148M, heavy alcohol consumption, and obesity – may be important to examine in prevention trials targeting individuals at high risk for progression to HCC.

Both heavy alcohol consumption and obesity are recognized as independent risk factors for cirrhosis and HCC in the general population.[5–8] Among patients with advanced liver disease, including cirrhosis, continued heavy alcohol consumption and obesity during adulthood were associated with progression to HCC in other studies.[7,8] We did not find these independent associations in our dataset. Apart from being a valid and relatively novel finding in a cohort with predominantly non-viral hepatitis cirrhosis, there are at least three additional explanations for this finding. Although we use validated surveys for alcohol use, we cannot exclude measurement bias. Obesity and alcohol intake may also change

over time, altering the progression risk of cirrhosis to HCC, but only baseline behavioral risk factors were used to investigate the associations between the risk factors and HCC risk. Second, the small sample size, specifically the small number of HCC outcomes may have prevented achieving statistical significance for the otherwise suggestive risk estimates. Lastly, the comparator group for obesity contained a large proportion of patients who were overweight (31.6%), and the comparator group for current heavy alcohol contained a large proportion of patients with past or current non-heavy drinking (62.6%) and therefore the effects may have been diluted. On the other hand, our analyses of joint associations with *PNPLA3* suggest that the effect of obesity and alcohol on cirrhosis progression to HCC may depend on whether a patient carries the *PNPLA3* risk allele. Therefore, it is possible that whether or not obesity and alcohol are found to be independently associated with HCC in any study may depend on the distribution of *PNPLA3* risk allele in that study cohort.

In our study, the magnitude of the association with current heavy alcohol consumption was enhanced in the presence of one additional risk factor (i.e., obesity, *PNPLA3*), suggesting a two-hit model for HCC risk. Therefore, the alcohol-HCC risk observed in population studies may be mostly explained by the formation of cirrhosis with minimal additional independent risk.

The strengths of our study include the well-defined cirrhosis etiology and diverse racial/ethnic backgrounds as well as uniform prospective BMI and alcohol measurements, and inclusion of genetic data. Ours is the first study that used data from two cohorts of contemporary, multi-ethnic patients with cirrhosis in the U.S. to longitudinally investigate the synergistic roles of *PNPLA3*, alcohol consumption and obesity on HCC risk. Given the racial and ethnic diversity of our cirrhosis cohorts, we were able to evaluate whether synergistic interactions are observed in populations with different genetic ancestries.

Our study has limitations. Despite prospective data collection, we cannot rule out misclassification bias in cirrhosis etiology. For example, MASLD diagnosis was defined based on the absence of other active risk factors (HCV or alcohol) but not based on demonstration of fatty liver disease, which is difficult to ascertain in the setting of cirrhosis. However, most patients classified as MASLD had a physician-documented diagnosis of MASLD and had at least one metabolic risk factor, providing support to our definition.[22] Our analyses aimed to examine for evidence of additive interaction or synergy between risk factors and not statistical interaction. Interaction measured on the additive scale (i.e., additive interaction) has been argued to correlate better with biologic interaction than when measured on the multiplicative scale (statistical interaction, which is commonly evaluated by including a product-term between two exposures of interest in the model).[26]

In summary, our study showed synergistic interplay between the *PNPLA3* risk allele with each of heavy alcohol consumption and obesity in regard to risk of developing HCC in patients with cirrhosis. The *PNPLA3* I148M variant status may help refine risk stratification and prognostication for HCC in patients with cirrhosis with heavy alcohol consumption who may need specific preventive measures. However, future studies are needed for additional external validation and refinement of risk stratification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What You Need to Know

Background

Risk of progression to hepatocellular carcinoma in patients with cirrhosis is not uniform. Identifying novel risk factors may help reduce cancer-related mortality among these patients.

Findings

In this cohort study of contemporary patients with cirrhosis from multiple etiologies, patients with cirrhosis who were carriers of the PNPLA3 risk allele and had a history of heavy alcohol consumption or obesity had excess risk of progression to HCC.

Implications for patient care

The PNPLA3 risk variant may help refine risk stratification for HCC, such that carriers who are also obese or current heavy alcohol drinkers may need specific preventive measures.

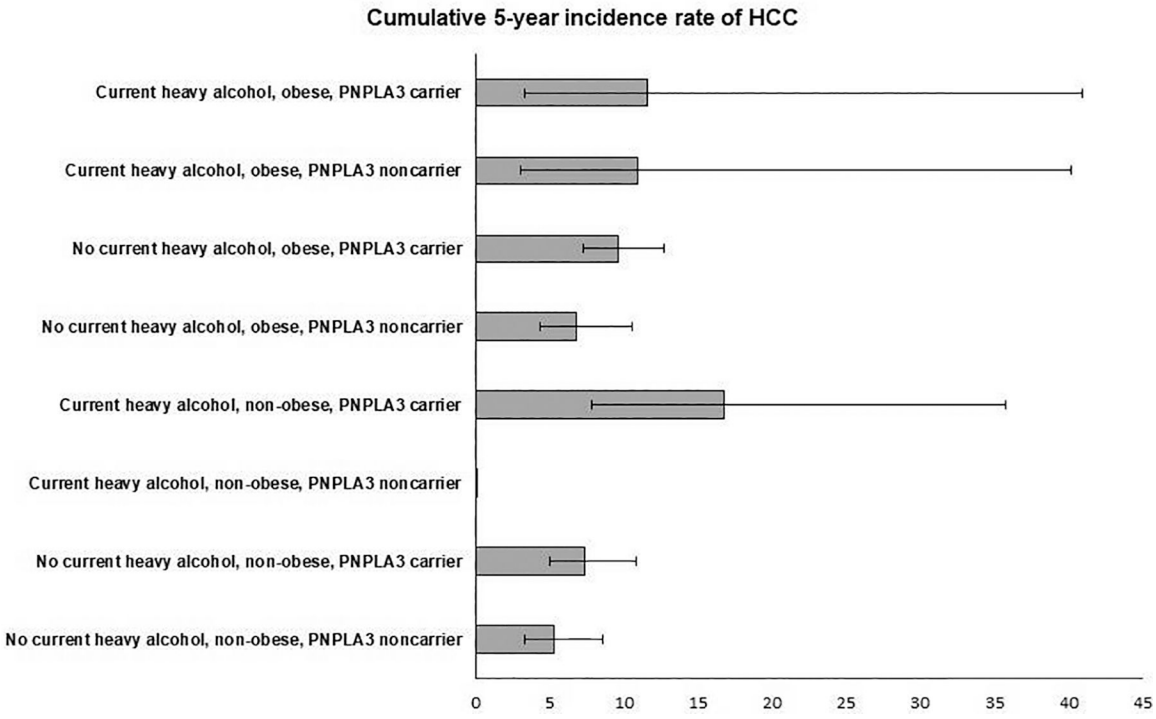

Figure 1.

Cumulative 5-year incidence of HCC among patients with cirrhosis according to joint associations of *PNPLA3* I148M variant, current heavy alcohol consumption, and obesity.

Table 1.

Clinical and epidemiological characteristics for the study cohort of 1,911 patients with cirrhosis.

Characteristic	n (%)
Age, mean±SD	59.56±10.02
Gender	
Female	682 (35.69%)
Male	1229 (64.31%)
Race and ethnicity	
NH-White	963 (50.39%)
NH-Black	350 (18.32%)
Hispanic	548 (28.68%)
Others	50 (2.62%)
Smoking	
Never	778 (40.71%)
Former	734 (38.41%)
Current	391 (20.46%)
Missing	8 (0.42%)
Current heavy alcohol use	
No	1785 (93.41%)
Yes	118 (6.17%)
Missing	8 (0.42%)
Hypertension	
No	938 (49.08%)
Yes	973 (50.92%)
Dyslipidemia	
No	1252 (65.52%)
Yes	659 (34.48%)
Diabetes	
No	1076 (56.31%)
Yes	835 (43.69%)
Obesity	
No (BMI<30)	933 (48.82%)
Yes (BMI>=30)	973 (50.92%)
Missing	5 (0.26%)
Cirrhosis Etiology	
Alcohol-related	320 (16.75%)
Autoimmune	143 (7.48%)
Hepatitis C active	255 (13.34%)
Hepatitis C cured	513 (26.84%)
Hepatitis B chronic	31 (1.62%)

Characteristic	**n (%)**
MASLD	591 (30.93%)
Others	58 (3.04%)
***PNPLA3*, rs738409**	
Noncarrier [0]	795 (41.6%)
Carrier [1, 2]	1116 (58.4%)

Table 2.

Associations between demographic, etiological, and lifestyle factors and risk of incident HCC among patients with cirrhosis.

		Crude HR (95% CI)	P-value	Adjusted HR** (95% CI)	P-value
Age, years					
	<55	1.00 (ref)		1.00 (ref)	
	55–<65	1.86 (1.07–3.21)	0.0266	1.87 (1.03–3.41)	0.0397
	≥65	2.08 (1.19–3.62)	0.0097	2.26 (1.25–4.08)	0.0072
Sex					
	Female	1.00 (ref)		1.00 (ref)	
	Male	1.57 (1.04–2.37)	0.0334	1.58 (1.03–2.44)	0.0364
Race/ethnicity					
	NH-White	1.00 (ref)		1.00 (ref)	
	NH-Black	0.57 (0.33–1.00)	0.0512	0.47 (0.26–0.85)	0.0118
	Hispanic	0.81 (0.53–1.24)	0.3355	0.85 (0.55–1.32)	0.4746
	Others	0.56 (0.14–2.29)	0.4230	0.68 (0.17–2.74)	0.5831
HCV status*					
	No	1.00 (ref)		1.00 (ref)	
	Yes	1.49 (1.04–2.15)	0.0314	1.66 (1.13–2.44)	0.0102
PNPLA3 G risk allele carrier status					
	Noncarrier	1.00 (ref)		1.00 (ref)	
	Carrier	1.51 (1.02–2.22)	0.0379	1.62 (1.08–2.45)	0.0210
Current heavy alcohol consumption					
	No	1.00 (ref)		1.00 (ref)	
	Yes	1.41 (0.73–2.72)	0.3058	1.43 (0.75–2.75)	0.2774
Obesity					
	No	1.00 (ref)		1.00 (ref)	
	Yes	1.32 (0.91–1.90)	0.1444	1.37 (0.94–2.00)	0.0976

*Active or cured HCV infection.

** Full model included all terms in the table.

Table 3.

Joint association of *PNPLA3* I148M variant, current heavy alcohol consumption, and obesity with risk of incident HCC among patients with cirrhosis.

	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Alcohol use & *PNPLA3* genotype *				
No current heavy, noncarrier	1.00 (ref)		1.00 (ref)	
No current heavy, carrier	1.42 (0.95–2.13)	0.0848	1.54 (1.01–2.35)	0.0467
Current heavy, noncarrier	0.77 (0.18–3.21)	0.7180	0.86 (0.21–3.54)	0.8367
Current heavy, carrier	2.58 (1.18–5.63)	0.0172	2.65 (1.20–5.86)	0.0158
BMI & *PNPLA3* genotype **				
Non-obese, noncarrier	1.00 (ref)		1.00 (ref)	
Non-obese, carrier	1.70 (0.94–3.05)	0.0775	1.83 (1.01–3.35)	0.0482
Obese, noncarrier	1.45 (0.76–2.77)	0.2580	1.51 (0.79–2.90)	0.2117
Obese, carrier	2.01 (1.15–3.49)	0.0139	2.40 (1.33–4.31)	0.0035
Alcohol use & BMI ***				
Non-obese, no current heavy	1.00 (ref)		1.00 (ref)	
Non-obese, current heavy	1.61 (0.67–3.84)	0.2841	1.50 (0.63–3.55)	0.3569
Obese, no current heavy	1.36 (0.92–2.00)	0.1209	1.38 (0.93–2.05)	0.1066
Obese, current heavy	1.82 (0.65–5.09)	0.2566	1.88 (0.68–5.19)	0.2247

*Adjusted for age, gender, race/ethnicity, HCV, and BMI (obesity)

**Adjusted for age, gender, race/ethnicity, HCV, and alcohol consumption

***Adjusted for age, gender, race/ethnicity, HCV, and *PNPLA3* gene

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