Received: 31 January 2024 | Accepted: 3 March 2024

DOI: 10.1097/HC9.0000000000000441

ORIGINAL ARTICLE

OPEN

PNPLA3 risk allele is associated with risk of hepatocellular carcinoma but not decompensation in compensated cirrhosis

Esteban Urias[1] | Nicholas R. Tedesco[2] | Daniel A. Burkholder[3] | Isabel J. Moran[4] | Matthew J. Miller[2] | Venkata Sai J. Jasty[1] | Snehal Patil[5] | Sebastian Zoellner[5] | Karn Wijarnpreecha[6] | Vincent L. Chen[2]

[1]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA

[2]Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan, USA

[3]Division of Gastroenterology and Hepatology, Houston Methodist Hospital, Houston, Texas, USA

[4]Michigan State University College of Medicine, East Lansing, Michigan, USA

[5]Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA

[6]Department of Medicine, Division of Gastroenterology and Hepatology, University of Arizona College of Medicine—Phoenix, Phoenix, Arizona, USA

Correspondence
Vincent L. Chen, Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA.
Email: vichen@med.umich.edu

Abstract

Background: The *PNPLA3*-rs738409-G, *TM6SF2*-rs58542926-T, and *HSD17B13*-rs6834314-A polymorphisms have been associated with cirrhosis, hepatic decompensation, and HCC. However, whether they remain associated with HCC and decompensation in people who already have cirrhosis remains unclear, which limits the clinical utility of genetics in risk stratification as HCC is uncommon in the absence of cirrhosis. We aimed to characterize the effects of *PNPLA3*, *TM6SF2*, and *HSD17B13* genotype on hepatic decompensation, HCC, and liver-related mortality or liver transplant in patients with baseline compensated cirrhosis.

Methods: We conducted a single-center retrospective study of patients in the Michigan Genomics Initiative who underwent genotyping. The primary predictors were *PNPLA3*, *TM6SF2*, and *HSD17B13* genotypes. Primary outcomes were either hepatic decompensation, HCC, or liver-related mortality/transplant. We conducted competing risk Fine-Gray analyses on our cohort.

Results: We identified 732 patients with baseline compensated cirrhosis. During follow-up, 50% of patients developed decompensation, 13% developed HCC, 24% underwent liver transplant, and 27% died. *PNPLA3*-rs738409-G genotype was associated with risk of incident HCC: adjusted subhazard hazard ratio 2.42 (1.40–4.17), $p = 0.0015$ for *PNPLA3*-rs738409-GG vs. *PNPLA3*-rs738409-CC genotype. The 5-year cumulative incidence of HCC was higher in PNPLA3-rs738409-GG carriers than PNPLA3-rs738409-CC/-CG carriers: 15.6% (9.0%–24.0%) vs. 7.4% (5.2%–10.0%), $p < 0.001$. *PNPLA3* genotype was not associated with decompensation or

Abbreviations: aMAP, age-male-ALBI-platelets; MGI, Michigan Genomics Initiative; US, ultrasound.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepcommjournal.com.

the combined outcome of liver-related mortality or liver transplant. *TM6SF2* and *HSD17B13* genotypes were not associated with decompensation or HCC.

Conclusions: The *PNPLA3*-rs738409-G allele is associated with an increased risk of HCC among patients with baseline compensated cirrhosis. People with cirrhosis and *PNPLA3*-rs738409-GG genotype may warrant more intensive HCC surveillance.

BACKGROUND

Cirrhosis is a leading cause of death in chronic liver disease, with about 2.4% of global deaths attributed to it in 2019.[1] Although patients with compensated cirrhosis may be minimally symptomatic, they are at high risk of HCC and hepatic decompensation with ascites, variceal bleeding, and HE. Patients with compensated cirrhosis have a 5%–7% risk of decompensation per year and 42% over 10 years,[2,3] as well as a 1%–4% annual risk of developing HCC depending on the etiology of liver disease.[2,4] Remarkably, the risk of death increases from <5% annually in compensated cirrhosis to up to 50% annually after developing complications from hepatic decompensation.[5]

Genetics plays an important role in hepatic fibrosis and cirrhosis. Genome-wide or exome-wide association studies have identified several variants genotypes associated with advanced liver disease, including variants in the genes *PNPLA3*, *TM6SF2*, and *HSD17B13*, which have been associated with risk of cirrhosis, liver-related events, and HCC.[6–12] Most studies on these variants have focused on the general population, and they have been shown to influence the risk of cirrhosis and HCC.[13] However, the effects of these variants in individuals who already have compensated cirrhosis are less well studied. Importantly, all three of these variants are also associated with hepatic steatosis and fibrosis, raising the possibility that its effects on hepatic decompensation are mediated by its effects on steatosis/fibrosis. Whether these variants are associated with hepatic decompensation and HCC in people who already have cirrhosis, that is, whether they affect portal hypertensive physiology and directly result in carcinogenesis, remains less clear. A few studies showed an increased risk of liver-related death, ascites, and HCC in patients with cirrhosis in the homozygous *PNPLA3*-rs738409-GG variant.[14] Similarly, the *TM6SF2*-rs58542926-T variant has been associated with fibrosis progression, HCC, hepatic decompensation, and liver-related death in patients with advanced chronic liver disease though this effect was modest.[15] Its effect on individuals with underlying cirrhosis is not well understood, but interestingly, one recent study found that the variant increases the risk of decompensation and death in patients with cirrhosis.[16]

Here, we aimed to explore the potential clinical utility of genotyping to identify individuals with baseline compensated cirrhosis who are at high risk of HCC or decompensation and who might warrant more aggressive surveillance or treatment. In this study, we aimed to characterize the effects of *PNPLA3*, *TM6SF2*, and *HSD17B13* genotypes on hepatic decompensation, HCC, and a combined outcome of liver transplant or liver-related death in patients with baseline compensated cirrhosis.

METHODS

Ethics

This study was approved by the Institutional Review Board of the University of Michigan (Ann Arbor, MI). Michigan Genomics Initiative (MGI) participants provided written informed consent.

Cohort and genotyping

MGI is a prospective cohort recruiting from patients receiving routine medical care at Michigan Medicine (Ann Arbor, MI). At the time of analysis, it included >90,000 participants. Participants undergo whole blood genotyping on an Illumina HumanCoreExome v.12.1 array, a combined genome-wide association study and exome array consisting of >500,000 single nucleotide polymorphisms.[17] Imputation was performed to the Haplotype Reference Consortium panel (release 1 for chromosomes 1-22).[18] Please note that not all MGI patients have been genotyped at the time of analysis.

Liver phenotypes

Liver phenotypes were identified as described.[19] In brief, we screened within MGI for cirrhosis based on a combination of diagnostic codes for cirrhosis and portal hypertension (Supplemental Table S1, http://links.lww.

com/HC9/A880), endoscopic evidence of varices, elevated liver stiffness on vibration-controlled transient elastography (> 12 kPa), and imaging or biopsy evidence of cirrhosis. We then manually reviewed all flagged patients to confirm the presence and dates of cirrhosis, varices, and hepatic decompensation (Daniel A. Burkholder, Isabel J. Moran, and Matthew J. Miller). We included all patients in MGI confirmed to have baseline compensated cirrhosis.

Outcomes

In survival analyses, the primary predictors were the *PNPLA3*-rs738409-G, *TM6SF2*-rs58542926-T, and *HSD17B13*-rs6834314-A alleles. The primary outcomes were hepatic decompensation, HCC, and the combined endpoint of liver transplant or liver-related death. We conducted survival analyses using Fine-Gray competing risk analyses.[20] The index date was defined as the date the patient was diagnosed with cirrhosis. For the outcomes of HCC or decompensation, the competing risk was death without HCC or without decompensation, respectively. For the outcome of liver transplant or liver-related death, the competing risk was non–liver-related death. We used a 180-day landmark for all 3 analyses to take into account the delay in the detection of endpoints due to asymptomatic patients and the time lag to obtain diagnostic imaging, especially in HCC. We conducted subgroup analyses based on cirrhosis etiology, diabetes status, and age-male-ALBI-platelets (aMAP) score.[21,22] All models were adjusted for age, sex, disease etiology (viral, alcohol-associated, both viral and alcohol-associated, and nonviral nonalcoholic-associated) except for the etiology-specific subgroup analyses, and genetic principal components 1–10 to account for differences in ancestry.

Statistics

Quantitative variables were reported as median (interquartile range). Categorical variables were reported as percentages. Three-way comparisons of continuous variables were performed with Kruskal-Wallis statistics, and categorical variables were compared with a chi-squared statistic using Fisher test for the variable race.

Analyses were conducted using R version 4.0.2 (Vienna, Austria) with competing risk analyses conducted using the cmprsk package. A 2-sided p-value <0.05 was used to determine statistical significance throughout.

RESULTS

Cohort

We screened 3,280 MGI participants with potential cirrhosis who had undergone genotyping. Of these, 2160 did not truly have cirrhosis, and 288 had decompensated cirrhosis at the index date, resulting in a final cohort of 732 patients who met inclusion criteria.

Baseline characteristics

The median age of our cohort was 58 years; 43% were female and 91% were White (Table 1). The mean follow-up time was 6.6 years. The etiology of liver disease was 16% viral hepatitis, 18% alcohol-associated liver disease, 56% nonviral nonalcohol-associated liver disease, and the remainder had mixed etiologies. The baseline laboratory values were as expected for a cohort of patients with baseline compensated cirrhosis with a median Model for End-Stage Liver Disease 3.0 of 9.6, platelet count of 140 M/L, and normal bilirubin. There were no significant differences in disease etiology, laboratory values, or comorbidities between the different *PNPLA3* genotypes. During follow-up, 50% of patients developed decompensation, 13% developed HCC, 24% underwent liver transplant, and 27% died.

Effects of PNPLA3 on hepatic decompensation, HCC, and liver-related mortality/liver transplant

We evaluated the effects of *PNPLA3* genotype on HCC, decompensation, and liver transplant or liver-related mortality. *PNPLA3*-rs738409-G was associated with risk of incident HCC with adjusted subhazard ratio 2.42 (1.40–4.17), $p = 0.0015$ for *PNPLA3*-rs738409-GG versus *PNPLA3*-rs738409-CC genotype (Table 2). *PNPLA3*-rs738409-G was not associated with hepatic decompensation or liver-related death/transplant.

The 5-year cumulative incidence of HCC was higher in PNPLA3-rs738409-GG carriers than PNPLA3-rs738409-CC/-CG carriers: 15.6% (9.0%–24.0%) versus 7.4% (5.2%–10.0%), $p < 0.001$ (Figure 1 and Table 3). However, there was no significant difference between the 5-year cumulative incidence of decompensation ($p = 0.42$) or liver-related mortality or liver transplant ($p = 0.74$; Figure 1 and Supplemental Figure S1, http://links.lww.com/HC9/A880). When we stratified individuals by etiology of cirrhosis, there was a significant difference in HCC 5-year cumulative incidence for *PNPLA3*-rs738409-CC/-CG versus *PNPLA3*-rs738409-GG carriers in alcohol-associated liver disease (9.7% [5.2%–15.8%) vs. 17.1% (5.2%–35.0%), $p = 0.044$] and nonviral nonalcohol-related liver disease [4.3% (2.3%–7.3%) versus 15.4% (7.5%–25.9%), $p = 0.0001$], but not in viral hepatitis ($p = 0.18$; Table 3). When the patients were stratified by aMAP score subgroups, there were zero cases of HCC in the aMAP < 50 groups, regardless of *PNPLA3* genotype (Table 3). There were also zero cases for the *PNPLA3*-rs738409-CC/-CG and aMAP ≥ 50 and ≤ 60 groups.

TABLE 1 Baseline clinical characteristics based on *PNPLA3*-rs738409 genotype.

Characteristic	CC (N = 327)	CG (N = 290)	GG (N = 115)	*p*
Demographics				
Male, n (%)	186 (56.9)	171 (59.0)	63 (54.8)	0.72
Age	57.4 (47.9–64.6)	58.1 (49.4–64.3)	56.7 (47.5–64.2)	0.74
Race/ethnicity, n (%)	—	—	—	< 0.001
White	292 (89.3)	269 (92.8)	106 (92.2)	—
Black	25 (7.6)	2 (0.7)	2 (1.7)	—
Hispanic	3 (0.9)	6 (2.1)	3 (2.6)	—
Asian	7 (2.1)	13 (4.5)	4 (3.5)	—
Comorbidities				
Body mass index (kg/m^2)	30.3 (26.3–34.8)	31.0 (26.2–35.8)	32.6 (27.4–38.9)	0.012
Type 2 diabetes, n (%)	173 (52.9)	154 (53.1)	60 (52.2)	0.99
Hypertension, n (%)	223 (68.2)	201 (69.3)	80 (69.6)	0.94
Hyperlipidemia, n (%)	155 (47.4)	145 (50.0)	55 (47.8)	0.80
Etiology, n (%)	—	—	—	0.084
Alcohol	50 (15.3)	57 (19.7)	21 (18.3)	—
Viral	65 (19.9)	41 (14.1)	12 (10.4)	—
Both	31 (9.5)	34 (11.7)	8 (7.0)	—
Neither	181 (55.4)	158 (54.5)	74 (64.3)	—
Esophageal varices	145 (44.3)	134 (46.2)	67 (58.3)	0.030
Model for End-Stage Liver Disease 3.0	10 (8–13)	10 (8–14)	9 (8–15)	0.86
Laboratory values				
Alanine aminotransferase (U/L)	42 (26–74)	45 (28–83)	40 (26–57)	0.42
Aspartate aminotransferase (U/L)	49 (32–83)	54 (35–83)	49 (35–66)	0.42
Alkaline phosphatase (U/L)	123 (88–173)	111 (84–165)	118 (86–161)	0.42
Total bilirubin (mg/dL)	0.80 (0.50–1.42)	0.80 (0.50–1.30)	0.80 (0.50–1.50)	0.88
Platelet count (K/μL)	141 (104–209)	140 (94–206)	138 (90–184)	0.32
Creatinine (mg/dL)	0.85 (0.70–1.05)	0.88 (0.70–1.08)	0.80 (0.68–1.00)	0.32
International normalized ratio	1.05 (1.03–1.09)	1.05 (1.01–1.10)	1.09 (1.04–1.17)	0.38
Sodium (mmol/L)	139 (138–141)	139 (137–141)	140 (138–141)	0.61
Hemoglobin A1c (%)	6.9 (5.6–7.8)	6.5 (5.5–8.2)	6.3 (5.5–8.3)	0.94
White blood cell count (K/uL)	6.1 (4.7–8.0)	6.5 (4.8–8.1)	5.7 (4.5–6.9)	0.049
Hemoglobin (g/dL)	12.9 (11.6–14.3)	13.6 (12.0–14.8)	12.95 (10.9–14.3)	0.0053

Note: Three-way comparisons of continuous variables were performed with Kruskal-Wallis statistics, and comparisons of categorical variables were performed using a chi-squared statistic using Fisher test for the variable race. Quantitative variables were reported as median (interquartile range) and categorical variables were reported as percentages.

Otherwise, there was a significant difference in HCC 5-year cumulative incidence for *PNPLA3*-rs738409-CC/-CG vs. *PNPLA3*-rs738409-GG carriers in the aMAP ≥ 50 groups (7.9% [5.5%–10.8%] versus 14.5% [7.9%–23.0%], $p = 0.003$) and aMAP ≥ 60 group (9.0% [6.2%–12.3%] versus 14.7% [7.7%–23.7%], $p = 0.016$).

Effects of TM6SF2 and HSD17B13 on hepatic decompensation, HCC, and liver-related death/liver transplant

We performed similar analyses evaluating the impact of *TM6SF2*-rs58542926-T and *HSD17B13*-rs6834314-A genotypes on HCC, decompensation, and liver-related death/transplant. *TM6SF2*-rs58542926-T and *HSD17B13*-rs6834314-A risk variants were not associated with decompensation, HCC, or liver-related death/transplant (Supplemental Table S2, http://links.lww.com/HC9/A880). There were also no differences in the 5-year cumulative incidences between *TM6SF2* and *HSD17B13* risk variants (Supplemental Figure S2, http://links.lww.com/HC9/A880 and S3, http://links.lww.com/HC9/A880).

We performed similar analyses evaluating the impact of nine additional genotype variants that have been shown to be associated with cirrhosis in previous studies.[23] Only the alpha-1 antitrypsin deficiency-associated variant, *SERPINA1*-rs28929474-CT/TT,

TABLE 2 Effects of *PNPLA3* risk alleles on liver-related outcomes.

	HCC		Decompensation		Liver-related mortality or liver transplant	
***PNPLA3*-rs738409 genotype**	**Adjusted sHR**	***p***	**Adjusted sHR**	***p***	**Adjusted sHR**	***p***
CC	Referent	—	Referent	—	Referent	—
CG	1.08 (0.64–1.82)	0.76	1.16 (0.89–1.50)	0.27	1.07 (0.77–1.49)	0.69
GG	2.42 (1.40–4.17)	0.0015	1.21 (0.85–1.72)	0.30	0.89 (0.56–1.42)	0.63

Note: Effects are shown as adjusted subhazard ratios (95% CI) for *PNPLA3*-rs738409-CG or -GG relative to *PNPLA3*-rs738409-CC genotypes. Models were run as Fine-Gray competing risk analyses with death without HCC, death without decompensation, or non–liver-related death, respectively, as competing risks.
Abbreviation: sHR, subhazard ratio.

was associated with hepatic decompensation and transplant-free survival, consistent with our previous report.[19] All other variants had no difference in the 5-year cumulative incidence of HCC, decompensation, or liver-related mortality/transplant (Supplemental Figure S3, http://links.lww.com/HC9/A880).

DISCUSSION

We found that the *PNPLA3*-rs738409-G allele was associated with increased HCC incidence but not hepatic decompensation or liver-related mortality/transplant in patients with baseline compensated cirrhosis. This adds to the literature by showing that associations between the high-risk *PNPLA3* variant are not solely confounded by its effects on steatosis and fibrosis and may have a direct carcinogenic effect. The association between *PNPLA3* genotype and HCC remained concordant across most etiologies of liver disease except for viral hepatitis[24,25] and aMAP score.[21,22]

Based on our results, we believe genotyping may improve upon existing HCC surveillance recommendations and move toward precision health. Major professional associations recommend screening for HCC in most patients with cirrhosis every 6 months with an abdominal ultrasound, with or without serum alpha-fetoprotein.[26,27] However, there may be patients who do not require such intensive surveillance that can be costly and inconvenient and may result in false positives.[28,29] Conversely, there may be other patients with more aggressive disease biology who should undergo more intensive surveillance. Some polygenic risk stratification tools have already been proposed that use *PNPLA3* and other genotypes to identify individuals at high risk for HCC in the general population.[13] Genetics may also help inform optimal practice of surveillance in patients with cirrhosis. While there is no evidence that surveillance with United States every 3 months results in earlier HCC diagnosis or greater receipt of HCC treatment than United States annually[30,31] or every 6 months,[32] there may be subgroups, including those with higher genetic risk

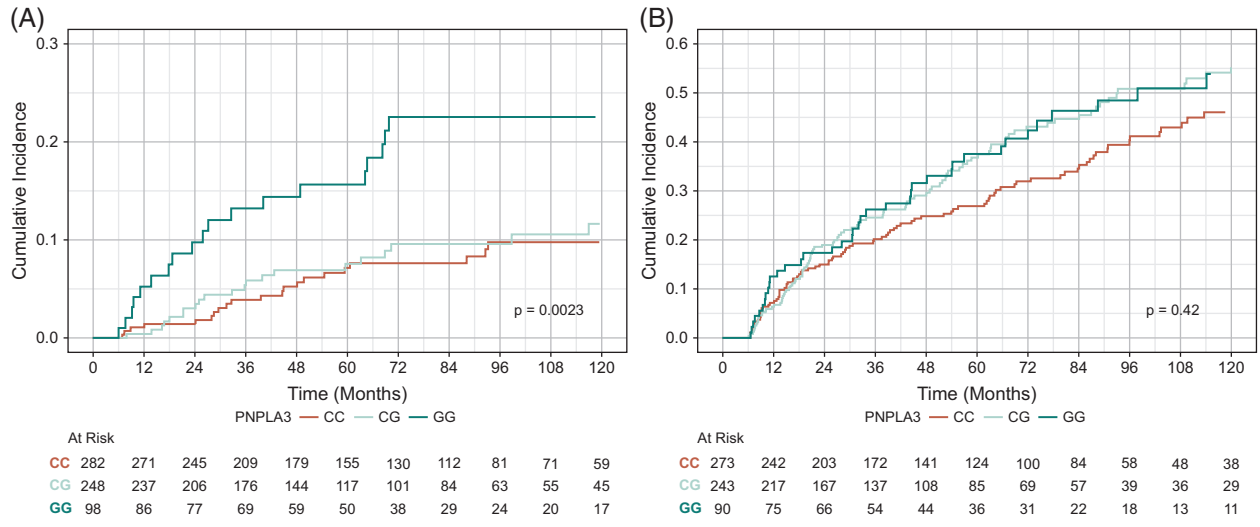

FIGURE 1 Effects of *PNPLA3* genotype on cumulative incidence of (A) HCC or (B) hepatic decompensation. Depicted are the effects of *PNPLA3*-rs738409-CC, CG, or GG genotype on the respective outcomes. Models were run as Fine-Grey competing risk models, with death without HCC or hepatic decompensation as the competing risk. Abbreviation: aMAP, age-male-ALBI-platelets.

TABLE 3 Effects of *PNPLA3* genotype on 5-year cumulative incidence of HCC.

	PNPLA3-rs738409 genotype				
	CC/CG		GG		
Cohort	Cases/total patients	5-y cumulative incidence (%)	Cases/total patients	5-y cumulative incidence	*p*
Full cohort	33/617	7.4 (5.2–10.0)	14/115	15.6 (9.0–24.0)	< 0.001
Viral hepatitis	18/171	15.0 (9.2–22.0)	3/20	21.4 (4.8–45.8)	0.18
Alcohol-associated liver disease	12/172	9.7 (5.2–15.8)	4/29	17.1 (5.2–35.0)	0.044
Nonviral nonalcoholic liver disease	11/339	4.3 (2.3–7.3)	9/74	15.4 (7.5–25.9)	< 0.001
Diabetes	20/327	8.2 (5.2–12.2)	12/60	23.8 (13.1–36.3)	0.0010
aMAP ≥ 50[a]	31/541	7.9 (5.5–10.8)	12/104	14.5 (7.9–23.0)	0.0029

Note: Incidence is shown as the 5-year cumulative incidence (95% CI) of HCC for *PNPLA3*-rs738409-GG relative to *PNPLA3*-rs738409-CC/-CG, and as total number of cases/patients. Models were run as Fine-Gray competing risk analyses with death without HCC as a competing risk. aMAP, age-male-ALBI-platelets score.
[a]There were no incident HCC cases in patients with aMAP < 50.
Abbreviation: aMAP, age-male-ALBI-platelets.

who may benefit from cross-sectional imaging with CT or abbreviated MRI.[33,34] Future prospective studies will be required to confirm our findings of higher HCC incidence in people with cirrhosis and high-risk *PNPLA3* genotype.

Mechanisms driving the associations between *PNPLA3* genotype and HCC remain unclear, although it is believed that the *PNPLA3* high-risk variant either affects specific carcinogenic pathways directly or creates an environment that promotes liver carcinogenesis through the dysregulation of metabolic pathways and production of proinflammatory and profibrogenic compounds from HSCs.[35] The *PNPLA3*-rs738409-G risk allele is also associated with more poorly differentiated HCC tumors, also supporting claims that it affects cancer biology.[36] Our results did not show an association between *PNPLA3* risk alleles and hepatic decompensation, and there is no clear mechanism described in previous studies that connects both of them. Although mortality and rates of liver-related events may be increased in patients with *PNPLA3* risk alleles and elevated portal pressures, there is a paucity of literature on how *PNPLA3* genotype would directly contributes to portal hypertension.[37]

This study had several limitations. Our study included a predominantly European-ancestry cohort, and the impact of *PNPLA3* genotype in other ancestries will have to be validated in other studies. The cohort was derived from a tertiary center with a high cumulative incidence of decompensation, suggesting that our patients had severe baseline disease. Additionally, this cohort had a high prevalence of obesity and diabetes, suggesting that many of them likely had a component of metabolic dysfunction-associated steatotic liver disease (perhaps unrecognized), which makes the generalizability of these results to individuals with "pure" viral or alcohol-associated cirrhosis unclear.

In conclusion, even among patients with baseline compensated cirrhosis, *PNPLA3* genotype is associated with an increased risk of HCC. This finding supports the idea that *PNPLA3* genotype directly influences carcinogenic mechanisms and may be relevant in risk stratification in people with cirrhosis.

ACKNOWLEDGMENTS

The authors acknowledge the Michigan Genomics Initiative participants, Precision Health at the University of Michigan, the University of Michigan Medical School Central Biorepository, the University of Michigan Advanced Genomics Core and the University of Michigan Medical School Data Office for Clinical and Translational Research for providing data and specimen storage, management, processing, and distribution services, and the Center for Statistical Genetics in the Department of Biostatistics at the School of Public Health for genotype data curation, imputation, and management in support of the research reported in this manuscript.

FUNDING INFORMATION

Vincent L. Chen was supported in part by NIDDK (K08 DK132312).

CONFLICTS OF INTEREST

Vincent L. Chen: Received grant funding from AstraZeneca and KOWA (to the University of Michigan). The remaining authors have no conflicts to report.

ORCID

Vincent L. Chen https://orcid.org/0000–0002–0157–6066

REFERENCES

1. Global health estimates: Leading causes of death. In: The Global Health Observatory. WHO; 2023.
2. D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: A 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther. 2014;39:1180–93.
3. Fleming KM, Aithal GP, Card TR, West J. The rate of decompensation and clinical progression of disease in people with cirrhosis: A cohort study. Aliment Pharmacol Ther. 2010;32: 1343–50.
4. Kanwal F, Khaderi S, Singal AG, Marrero JA, Loo N, Asrani SK, et al. Risk factors for HCC in contemporary cohorts of patients with cirrhosis. Hepatology. 2023;77:997–1005.
5. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol. 2006;44:217–31.
6. Kim HS, Xiao X, Byun J, Jun G, DeSantis SM, Chen H, et al. Synergistic associations of PNPLA3 I148M variant, alcohol intake, and obesity with risk of cirrhosis, hepatocellular carcinoma, and mortality. JAMA Netw Open. 2022;5:e2234221.
7. Trepo E, Caruso S, Yang J, Imbeaud S, Couchy G, Bayard Q, et al. Common genetic variation in alcohol-related hepatocellular carcinoma: A case-control genome-wide association study. Lancet Oncol. 2022;23:161–71.
8. Abul-Husn NS, Cheng X, Li AH, Xin Y, Schurmann C, Stevis P, et al. A protein-truncating HSD17B13 variant and protection from chronic liver disease. N Engl J Med. 2018;378:1096–6.
9. Buch S, Stickel F, Trepo E, Way M, Herrmann A, Nischalke HD, et al. A genome-wide association study confirms PNPLA3 and identifies TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis. Nat Genet. 2015;47:1443–8.
10. Ma Y, Belyaeva OV, Brown PM, Fujita K, Valles K, Karki S, et al. 17-Beta hydroxysteroid dehydrogenase 13 is a hepatic retinol dehydrogenase associated with histological features of non-alcoholic fatty liver disease. Hepatology. 2019;69:1504–9.
11. Chen VL, Chen Y, Du X, Handelman SK, Speliotes EK. Genetic variants that associate with cirrhosis have pleiotropic effects on human traits. Liver Int. 2020;40:405–15.
12. Chen VL, Oliveri A, Miller MJ, Wijarnpreecha K, Du X, Chen Y, et al. PNPLA3 genotype and diabetes identify patients with nonalcoholic fatty liver disease at high risk of incident cirrhosis. Gastroenterology. 2023;164:966–77 e917.
13. Gellert-Kristensen H, Richardson TG, Davey Smith G, Nordestgaard BG, Tybjaerg-Hansen A, Stender S. Combined effect of PNPLA3, TM6SF2, and HSD17B13 variants on risk of cirrhosis and hepatocellular carcinoma in the general population. Hepatology. 2020;72:845–56.
14. Guyot E, Sutton A, Rufat P, Laguillier C, Mansouri A, Moreau R, et al. PNPLA3 rs738409, hepatocellular carcinoma occurrence and risk model prediction in patients with cirrhosis. J Hepatol. 2013;58:312–8.
15. Balcar L, Scheiner B, Urheu M, Weinberger P, Paternostro R, Simbrunner B, et al. The impact of transmembrane 6 superfamily 2 (TM6SF2) rs58542926 on liver-related events in patients with advanced chronic liver disease. Dig Liver Dis. 2023;55:1072–80.
16. Gil-Gomez A, Rojas A, Garcia-Lozano MR, Munoz-Hernandez R, Gallego-Duran R, Maya-Miles D, et al. Impact of a loss-of-function variant in HSD17B13 on hepatic decompensation and mortality in cirrhotic patients. Int J Mol Sci. 2022;23:11840.
17. Dey R, Schmidt EM, Abecasis GR, Lee S. A fast and accurate algorithm to test for binary phenotypes and its application to PheWAS. Am J Hum Genet. 2017;101:37–49.
18. Chen VL, Du X, Chen Y, Kuppa A, Handelman SK, Vohnoutka RB, et al. Genome-wide association study of serum liver enzymes implicates diverse metabolic and liver pathology. Nat Commun. 2021;12:816.
19. Chen VL, Burkholder DA, Moran IJ, DiBattista JV, Miller MJ, Chen Y, et al. Hepatic decompensation is accelerated in patients with cirrhosis and alpha-1 antitrypsin Pi *MZ genotype. JHEP Rep. 2022;4:100483.
20. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94: 496–509.
21. Fan R, Papatheodoridis G, Sun J, Innes H, Toyoda H, Xie Q, et al. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol. 2020; 73:1368–78.
22. Johnson PJ, Innes H, Hughes DM, Kalyuzhnyy A, Kumada T, Toyoda H. Evaluation of the aMAP score for hepatocellular carcinoma surveillance: a realistic opportunity to risk stratify. Br J Cancer. 2022;127:1263–9.
23. Emdin CA, Haas M, Ajmera V, Simon TG, Homburger J, Neben C, et al. Association of genetic variation with cirrhosis: A multi-trait genome-wide association and gene-environment interaction study. Gastroenterology. 2021;160:1620–33 e1613.
24. Singal AG, Manjunath H, Yopp AC, Beg MS, Marrero JA, Gopal P, et al. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: A meta-analysis. Am J Gastroenterol. 2014;109:325–4.
25. Valenti L, Aghemo A, Stattermayer AF, Maggioni P, De Nicola S, Motta BM, et al. Implications of PNPLA3 polymorphism in chronic hepatitis C patients receiving peginterferon plus ribavirin. Aliment Pharmacol Ther. 2012;35:1434–42.
26. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68:723–50.
27. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69:182–236.
28. Atiq O, Tiro J, Yopp AC, Muffler A, Marrero JA, Parikh ND, et al. An assessment of benefits and harms of hepatocellular carcinoma surveillance in patients with cirrhosis. Hepatology. 2017;65:1196–205.
29. Singal AG, Tiro JA, Murphy CC, Blackwell JM, Kramer JR, Khan A, et al. Patient-reported barriers are associated with receipt of hepatocellular carcinoma surveillance in a multicenter cohort of patients with cirrhosis. Clin Gastroenterol Hepatol. 2021;19: 987–95 e981.
30. Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol. 2010;53:291–7.
31. Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: A randomized trial comparing 3- and 6-month periodicities. Hepatology. 2011;54:1987–97.
32. Pelizzaro F, Peserico G, D'Elia M, Cazzagon N, Russo FP, Vitale A, et al. Surveillance for hepatocellular carcinoma with a 3-months interval in "extremely high-risk" patients does not further improve survival. Dig Liver Dis. 2022;54:927–36.
33. Park HJ, Kim SY, Singal AG, Lee SJ, Won HJ, Byun JH, et al. Abbreviated magnetic resonance imaging vs ultrasound for surveillance of hepatocellular carcinoma in high-risk patients. Liver Int. 2022;42:2080–92.
34. Chen VL, Singal AG, Tapper EB, Parikh ND. Hepatocellular carcinoma surveillance, early detection and survival in a privately insured US cohort. Liver Int. 2020;40:947–55.
35. Bruschi FV, Claudel T, Tardelli M, Caligiuri A, Stulnig TM, Marra F, et al. The PNPLA3 I148M variant modulates the fibrogenic phenotype of human hepatic stellate cells. Hepatology. 2017;65: 1875–90.

36. Liu YL, Patman GL, Leathart JB, Piguet AC, Burt AD, Dufour JF, et al. Carriage of the PNPLA3 rs738409 C > G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol. 2014;61:75–81.
37. Mandorfer M, Scheiner B, Stattermayer AF, Schwabl P, Paternostro R, Bauer D, et al. Impact of patatin-like phospholipase domain containing 3 rs738409 G/G genotype on hepatic decompensation and mortality in patients with portal hypertension. Aliment Pharmacol Ther. 2018;48:451–9.

How to cite this article: Urias E, Tedesco NR, Burkholder DA, Moran IJ, Miller MJ, Jasty VSJ, et al. *PNPLA3* risk allele is associated with risk of hepatocellular carcinoma but not decompensation in compensated cirrhosis. Hepatol Commun. 2024;8:e0441. https://doi.org/10.1097/HC9.0000000000000441