Received: 26 July 2024 | Revised: 2 September 2024 | Accepted: 4 September 2024

DOI: 10.1111/liv.16103

Liver INTERNATIONAL WILEY

MINI REVIEW

Integrating *PNPLA3* into clinical risk prediction

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Handling Editor: Luca Valenti.

Abstract

The *PNPLA3*-rs738409-G variant was the first common variant associated with hepatic fat accumulation and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). Nevertheless, to date, the clinical translation of this discovery has been minimal because it has not yet been clearly demonstrated where the genetic information may play an independent and additional role in clinical risk prediction. In this mini-review, we will discuss the most relevant evidence regarding the potential integration of the *PNPLA3* variant into scores and algorithms for liver disease diagnostics and risk stratification, specifically focusing on MASLD but also extending to liver diseases of other etiologies. The *PNPLA3* variant adds little in diagnosing the current state of the disease, whether in terms of presence/absence of metabolic dysfunction-associated steatohepatitis or the stage of fibrosis. While it can play an important role in prediction, allowing for the early definition of risk profiles that enable tailored monitoring and interventions over time, this is most valuable when applied to populations with relatively high pre-test probability of having significant fibrosis based on either non-invasive tests (e.g. Fibrosis-4) or demographics (e.g. diabetes). Indeed, in this context, integrating FIB4 with the *PNPLA3* genotype can refine risk stratification, though there is still no evidence that genetic information adds to liver stiffness determined by elastography. Similarly, in patients with known liver cirrhosis, knowing the *PNPLA3* genotype can play a role in predicting the risk of hepatocellular carcinoma, while more doubts remain about the risk of decompensation.

KEYWORDS
APRI, FIB-4, genetics, non-invasive test, precision medicine, VCTE

1 | INTRODUCTION

The *PNPLA3*-rs738409-G variant, corresponding to the I148M protein mutation, was identified initially as a hepatic steatosis-promoting variant[1–5] especially in conjunction with risk behaviours and cardiometabolic risk factors.[6–8] Subsequent studies have also demonstrated associations with liver fibrosis/cirrhosis[9–14] and hepatocellular carcinoma.[15–20] There has been interest in incorporating genetics into clinical risk prediction, but how to make this most clinically relevant has been a challenge.

We will briefly describe some of the potential applications that we believe are *less* relevant. First is the diagnosis of hepatic steatosis, which can already be accurately and inexpensively established using non-invasive methods such as ultrasound and the controlled attenuation parameter derived from vibration-controlled transient elastography (VCTE). In one of the few studies aimed at verifying

whether genetics improves blood-based diagnosis of steatosis, the addition of the *PNPLA3* genotype to a score including clinical (metabolic syndrome, type 2 diabetes mellitus [T2DM]) and biochemical (aminotransferases, insulin) parameters improved the accuracy of prediction by only 1%.[21] A second application of unclear utility is detection of fibrosis stage based on the *PNPLA3* genotype. In a cohort of 703 patients with histologically diagnosed MASLD from 7 European tertiary centers, higher diagnostic accuracy for advanced fibrosis was obtained if the *PNPLA3* rs738409 and *TM6SF2* rs58542926 variants, but not the *HSD17B13* rs72613567 one, were added to a baseline model including only clinical variables.[22] However, this benefit was again modest with C-statistic increasing from .78 without genetics to .79 with the *PNPLA3* genotype included.

In our opinion, there are several more promising potential applications: (1) diagnosis of steatohepatitis, for which accurate noninvasive tests are still lacking, (2) incremental addition of *PNPLA3* genotype to noninvasive tests in risk stratification of metabolic dysfunction-associated steatotic liver disease (MASLD) without known cirrhosis, and (3) prediction of risk of hepatocellular carcinoma (HCC) and hepatic decompensation in patients with cirrhosis (Figure 1). In this mini-review, we will address each of these topics in turn.

Key points

- The *PNPLA3* genotype is associated with the incidence of liver-related events, but whether it can be beneficial for clinical risk prediction beyond existing scores is less clear.
- In patients without cirrhosis, *PNPLA3* genotype provides incremental value to Fibrosis-4 score for prediction of incident severe liver disease, especially in patients who have at least intermediate Fibrosis-4 scores or risk factors such as type 2 diabetes mellitus. The incremental benefit over imaging-based non-invasive tests is not established.
- In patients with cirrhosis, *PNPLA3* genotype is associated with higher risk of hepatocellular carcinoma and may add incremental value beyond scores such as aMAP. This association is more consistent in steatotic liver disease.

2 | DIAGNOSIS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

A number of studies have used the genetic information for the diagnosis of metabolic dysfunction-associated steatohepatitis (MASH), for which liver biopsy is still the only method endorsed in guidance documents.[23,24] Hyysalo et al. derived and validated a score including *PNPLA3* genotype, aspartate aminotransferase (AST), and fasting insulin, which predicted histological MASH with relatively high accuracy in two cohorts of Finnish and Italian subjects (AUROC .77 and .76, respectively).[25] In a Korean population of 453 patients with biopsy-proven MASLD, divided into derivation and validation cohorts, a scoring system based on *PNPLA3* and *TM6SF2* genotypes, T2DM status, insulin resistance, and levels of AST and high-sensitivity C-reactive protein identified MASH with an AUROC of .86 in derivation and .78 in validation cohorts.[26] Genetic information has also been included in the NASH ClinLipMet Score[27] which includes *PNPLA3* genotype, AST and insulin levels, and a series of metabolites obtained through mass spectrometry; this score identified patients with MASH with an AUROC of .87, but the requirement of metabolomic data limits wider applicability.

Due to limitations of blood-based markers alone for the diagnosis of MASH, more recent attention has focused on the possibility of achieving a noninvasive imaging-derived diagnosis of fibrotic MASH, that is, MASH with at least 4 points of necro-inflammatory activity score and F2 fibrosis, as this diagnosis represents the entry point for trials with new MASH drugs. The most promising developments in this direction have been obtained with scores that integrate AST levels with results from other instrumental tests, such as the Fibroscan-AST (FAST) score and the MRI-AST (MAST) score.[28] Whether the inclusion of the *PNPLA3* genotype, or genetic information synthesized by polygenic risk scores (PRSs), in imaging-based scores provides additional benefit remains to be determined and in our view will determine whether *PNPLA3* is ultimately relevant in non-invasive diagnosis of MASH.

3 | RISK STRATIFICATION IN PERSONS WITHOUT CIRRHOSIS

The *PNPLA3* genotype and, more generally, the genetic information may play a more significant role in predicting liver-related events (LREs) than in characterizing the precise phenotype across the MASLD spectrum.[29] Several studies have reported that the *PNPLA3* genotype is associated with increased incidence of LREs and mortality in the overall population,[30–32] individuals with cardiometabolic risk factors,[33] and in patients with MASLD[34–36] (Table 1). It has also been associated with an increased risk of progression defined by changes in vibration-controlled transient elastography (VCTE)-derived scores.[39] However, to facilitate more routine incorporation of *PNPLA3* genotyping into practice, it is important to show that the genotype is associated with clinically relevant outcomes independent of established clinical risk scores. Furthermore, it is important to understand if, in addition to being associated with an increased risk of developing LREs, genetic information also provides a tangible advantage in terms of predictive accuracy. We will focus on the general population (including those with cardiometabolic comorbidities without necessarily having known liver disease) and MASLD.

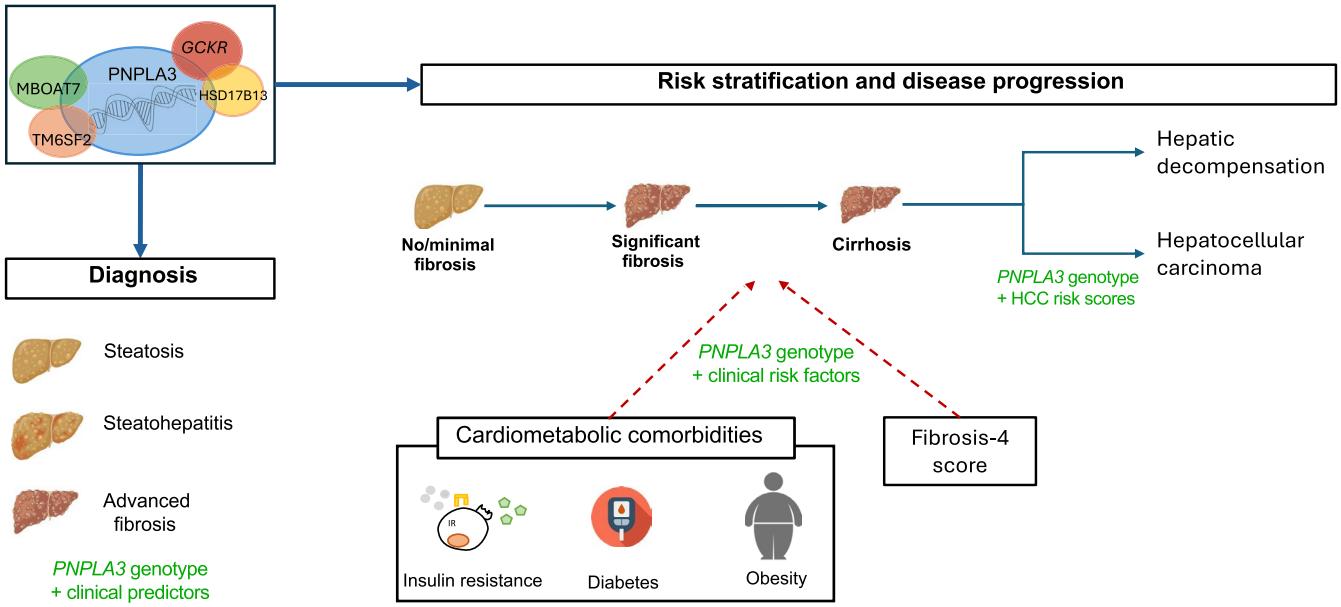

FIGURE 1 The role of the *PNPLA3* risk variant in clinical risk prediction. Schematic of the role of *PNPLA3* genotype in risk prediction. The top left shows *PNPLA3* as well as other key liver steatosis/fibrosis-associated variants (*TM6SF2*, *MBOAT7*, *GCKR*, *HSD17B13*). The bottom left illustrates reported potential uses of the *PNPLA3* genotype in diagnosis, including in combination with routine clinical predictors. The right side illustrates reported potential uses of the *PNPLA3* genotype in characterizing the disease trajectory of liver disease, especially metabolic dysfunction-associated steatotic liver disease, from early-stage (no/minimal fibrosis) to significant fibrosis to cirrhosis then hepatic decompensation and hepatocellular carcinoma (HCC). For the transition from significant fibrosis to cirrhosis, *PNPLA3* genotype utility has especially been reported when considered in conjunction with clinical risk factors such as cardiometabolic comorbidities (insulin resistance, diabetes, and/or obesity) and/or Fibrosis-4 score. Additional, *PNPLA3* has been reported to have utility in predicting decompensation and hepatocellular carcinoma in patients with established cirrhosis, including in conjunction with HCC risk scores.

3.1 | General population

Starting from the general population, in the Study of Health in Pomerania in North-Eastern Germany, the rs738409 *PNPLA3* variant was associated with a fourfold increase in the hazard ratio (HR) for liver disease-related mortality for men only, likely due to the small sample size, shorter follow-up, and fewer events in women.[30] These findings are consistent with those reported by Unalp-Arida et al. with data derived from the U.S. National Health and Nutrition Examination Survey, where the heterozygous *PNPLA3* CG genotype (HR ~3) and the homozygous GG genotype (HR ~18) were significantly associated with liver-disease mortality.[32] However, despite the clear association of certain genetic variants with an increased risk of LREs, the practical utility of genetic information in improving predictive accuracy for LREs at the population level has been strongly questioned. Innes et al. systematically reviewed commonly-used noninvasive scores for liver fibrosis and evaluated their impact on 1o-year risk of liver-related events in the community-based UK Biobank.[41] They then compared noninvasive scores with or without inclusion of a PRS for ability to predict 10-year risk of LREs. They found that among the widely used fibrosis scores such as fibrosis-4 (FIB4) and AST-platelet ratio index (APRI), there was minimal incremental benefit of incorporating genetics, with fraction of new prognostic information <.1. For example, the C-statistic for FIB4 increased from .78 to .79, and that of APRI increased from .804 to .809, with addition of the PRS. Thus, they concluded that there is minimal if any benefit to incorporating genetic risk into commonly-used risk scores to predict medium-term risk of liver-related events.

The question arises of whether genetics might perform better in a higher risk population. UK Biobank participants are notably 'healthier' than the overall population in terms of mortality, cardiometabolic comorbidities, and regular tobacco/alcohol use,[42] with a very low 10-year incidence of cirrhosis complications (.56% in the overall cohort). Indeed, an alternative perspective on the topic comes from a study published the same year, which also focused on UK Biobank participants, which arrived at somehow different conclusions.[37] In this work, a PRS based on variants in *PNPLA3* (rs738409), *TM6SF2* (rs58542926), *MBOAT7* (rs641738), and *GCKR* (rs780094) was found to improve risk stratification and prediction for LREs performed with classical clinical fibrosis scores. Nevertheless, unfavourable genetics did not affect the risk profile in subjects without metabolic risk factors or in the lower-risk fibrosis classes, while it did modulate the risk in those with both any metabolic risk and intermediate/high-risk profile by fibrosis scores.[37] Altogether, these data from population studies suggest that genetic information may have a significant impact on risk stratification, specifically when restricting the analysis to subjects who are dysmetabolic and/or have intermediate/advanced liver damage. Indeed, focusing on the general population but specifically on individuals with diabetes, Tavaglione et al. described a strong association between the *PNPLA3* variant and the occurrence of LREs (cirrhosis, decompensated liver disease, hepatocellular

TABLE 1 Selected studies associating *PNPLA3* genotype with occurrence of clinical outcomes in subjects from the general population with or without metabolic risk factors or with already diagnosed MASLD.

Study	Study type	Setting	Country	Outcome(s)	Results
Meffert et al.[30]	Retrospective	4.058 individuals from general population	Germany	Liver-related mortality	In men: per-allele, HR 4.27
Gellert-Kristensen et al.[31]	Retrospective	General population	110.761 individuals from Denmark (Copenhagen studies) and 334.691 individuals from UK (UK Biobank)	Cirrhosis, HCC	Cirrhosis: CG versus CC aOR 1.56 and 2.02 and GG versus CC 2.69 and 3.67 in Copenhagen studies and UK Biobank, respectively HCC: CG versus CC aOR 2.23 and 1.64 and GG versus CC 4.64 and 3.34 in Copenhagen studies and UK Biobank, respectively
Unalp-Arida et al.[32]	Retrospective	General population	13.298 individuals from U.S.A. (NHANES)	Liver-related mortality	Fully adjusted model: CG versus CC aOR 3.29 (p = n.s.) and GG versus CC aOR 19.1
Tavaglione et al.[33]	Retrospective	Subjects with T2DM from the general population	22.812 individuals from UK (UK Biobank)	Severe liver disease (cirrhosis, decompensation, HCC, liver failure and transplantation)	Additive model: HR 1.67 Recessive model: HR 2.32
De Vincentis et al.[37]	Retrospective	General population	266.687 individuals from UK (UK Biobank)	Severe liver disease (cirrhosis, decompensation, HCC, liver failure and transplantation)	Additive model: aHR 1.37 Dominant model: aHR 1.36 Recessive model: aHR 1.92
Pennisi et al.[38]	Retrospective analysis of prospectively-collected data	546 individuals with biopsy-or clinically-confirmed MASLD	Palermo (Italy)	Liver-related events in those with FIB4 ≥1.4	Dominant model: aHR .64 (p = n.s.) Interaction between PNPLA3 and T2DM HR 5.16
Koo et al.[39]	Retrospective analysis of prospectively-collected data	302 individuals with biopsy-confirmed MASLD	Korea	Progression of fibrosis [LSM ≥9.6 kPa for subjects with F0–2 at baseline; ΔLSM ≥20% for subjects with F3–4 at baseline]	GG versus CC: aHR 6.21 GC versus CC: aHR 4.04
Rosso et al.[35]	Retrospective analysis of prospectively-collected data	756 individuals with biopsy-confirmed MASLD	Italy	Liver-related events	In non-obese women older than 50 years and with fibrosis F3/F4: *PNPLA3* GG versus CC/CG 15.8% versus 0%, p = .005
Seko et al.[36]	Retrospective analysis of prospectively-collected data	1550 biopsy-confirmed MASLD subjects	Japan	Liver-related events	CG/GG versus CC: aHR 16.04

TABLE 1 (Continued)

Study	Study type	Setting	Country	Outcome(s)	Results
Chen et al.[40]	Retrospective analysis of prospectively-collected data	7.893 and 46.880 individuals with MASLD from general population (elevated ALT without other causes of liver disease)	U.S.A. (Michigan Genomics Initiative –MGI-) and UK (UK Biobank)	Cirrhosis	MGI: CG versus CC aHR 1.43 (p = n.s.) GG versus CC aHR 3.24 UK Biobank: CG versus CC aHR 1.05 (p = n.s.) GG versus CC aHR 1.99
Chalasani et al.[34]	Retrospective analysis of prospectively-collected data	2075 biopsy-confirmed MASLD cohort	U.S.A. (MASH Clinical Research Network)	Major adverse liver outcomes (MALO)	G-allele adj. sHR: 1.4 In those with advanced fibrosis: G-allele 85% versus noncarriers 53%, p = .03. Association between PNPLA3 and MALO greater among older than 60 years (sHR: 2.1), women (sHR: 1.4), AF (sHR: 1.9) and T2DM (sHR: 2.1)

Abbreviations: FIB4, fibrosis-4 index; HCC, hepatocellular carcinoma; HR, hazard ratio (aHR, adjusted-HR; sHR, sub-HR); LSM, liver stiffness measurement (ΔLSM, Delta-LSM); MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio (aOR, adjusted-OR); T2DM, type2 diabetes mellitus.

carcinoma, and/or liver transplantation), greater in the recessive than in the additive model analysis (aHR 2.3 vs. 1.7).[33]

3.2 | Patients with MASLD

In histologically-diagnosed MASLD cohorts, *PNPLA3* genotype may add information even beyond histologic fibrosis stage, as highlighted in two recent biopsy-based cohorts. A recent study from the United States MASH Clinical Research Network found that among 2075 patients, *PNPLA3*-rs738409-G allele carriage was associated with increased risk of major adverse liver outcomes (MALO), with sHR 1.51 and 1.94 for CG and GG genotypes versus CC, respectively. This difference was numerically larger in individuals with advanced fibrosis, with a cumulative incidence of 85% versus 58% in those with versus without the G allele during follow-up (difference = 27%), compared to 25% and 8% in those without baseline advanced fibrosis (difference = 17%).[34] Another study from a multicenter Japanese cohort with 1178 patients found an association between *PNPLA3* genotype and LREs in the overall cohort.[43] Again, the divergence in risk of LREs based on genetic risk appeared greater among the 238 patients with advanced fibrosis on biopsy (>50% vs. <20% at 10 years).[43]

As biopsy becomes less frequently employed, it is also important to determine whether the *PNPLA3* genotype adds information to non-invasive tests.[44] Insights in this direction have come from recent studies. One study by Pennisi et al. started with an Italian cohort of 546 patients with either a histologic diagnosis of MASLD, or liver stiffness measurement (LSM) by VCTE >11–11.5 kPA and ≥1 metabolic syndrome criterion.[38] Here, a combined genetic and metabolic staging system, including information on *PNPLA3*, *TM6SF2*, and *HSD17B13* genotypes, defined 5 risk classes with a markedly different cumulative incidence of LREs (at 5 years, from ~4% in the low-risk class to ~90% in the high-risk class).[38] This score was externally validated in UK Biobank participants with FIB4 ≥1.3 and demonstrated a >20-fold gradient in risk of severe liver disease. Another study by Chen et al. compared the addition of *the PNPLA3* genotype to routine clinical predictors for risk stratification in two cohorts, a hospital-based cohort in the US and UK Biobank participants, all of whom had chronically elevated alanine aminotransferase as a proxy of MASLD.[40,45] When focusing on the intermediate-risk FIB4 category (1.3–2.67), combining the highest-risk *PNPLA3* genotype (rs738409-GG) with diabetes status resulted in an overall incidence of cirrhosis that was not significantly different from that of individuals with high FIB4 (>2.67). That is, having diabetes and the highest risk *PNPLA3* genotype results in 'bumping up' one's risk category predicted by FIB4 alone. Another recent study assessed the impact of the *PNPLA3* genotype not on hard outcomes, but rather on the risk of advanced fibrosis measured by magnetic resonance elastography or VCTE.[46] The authors compared a PRS (including *PNPLA3* genotype) plus FIB4 to FIB4 alone. In a well-phenotyped cohort of 382 patients with type 2 diabetes, the authors found that reclassifying FIB4 <1.3 with high PRS as intermediate risk would mean that 21% of patients with advanced fibrosis would be prevented

from being miscategorized as having low risk. Notably, similarly to the focus on indeterminate FIB4 categories in the Pennisi and Chen studies above, this study evaluated a cohort with a high baseline prevalence of advanced fibrosis (12%).

We believe these studies highlight that while the *PNPLA3* genotype is likely not useful for risk stratification in the general population or in low-risk individuals, there may be some utility in at-risk populations such as those with intermediate FIB4 scores or older adults with obesity and/or T2DM.[47] This is consistent with the fact that adiposity, particularly abdominal adiposity, has been shown to amplify the effect of *PNPLA3* and other variants associated with MASLD.[48,49] The findings about the prognostic importance of *PNPLA3* in conjunction with FIB4 were identified retrospectively and will require prospective validation to determine the impact on outcomes.

3.3 | Hepatocellular carcinoma risk in MASLD

We will also briefly discuss HCC risk in non-cirrhotic populations based on *PNPLA3* genotype in MASLD. A case–control study by Liu et al.[20] of 375 patients with MASLD with or without HCC found that in a multivariate analysis adjusted for the most clinically relevant risk factors including cirrhosis, each *PNPLA3* variant allele was associated with a 2.2-fold increased risk of HCC presence, with GG homozygotes exhibiting a 5-fold increased risk over CC ones. Another study by Bianco et al. was conducted in two large cohorts of patients with NAFLD and in a general population cohort (UK Biobank).[50] Here, a polygenic risk score (PRS) including variants in *PNPLA3*, *TM6SF2*, *GCKR*, and *MBOAT7*, and then adjusted for *HSD17B13*, was associated with approximately a 9-fold increased odds ratio (OR) for HCC, and also a ~12-fold increased OR in those who had severe fibrosis. More interestingly, the PRS predicted HCC even in patients without severe fibrosis (OR ~2), and improved HCC detection in individuals aged over 40 years independently of severe fibrosis (OR 1.5). While these findings may identify a category of patients who merit closer surveillance, even in the absence of advanced fibrosis, it is unknown if there are non-cirrhotic subgroups defined by *PNPLA3* genotype and other risk factors with HCC incidence high enough to warrant screening.[51]

3.4 | Sex- and ancestry-specific effects

Finally, we find it appropriate to discuss some evidence suggesting a different impact of the *PNPLA3* variant on the development and natural history of MASLD depending on genetic ancestry and sex. Recent studies indeed show that the *PNPLA3* variant confers a much higher risk of MASLD-related clinical outcomes in individuals of Japanese ancestry, compared to what is observed in Europeans.[36] Asians have been shown to have a higher prevalence of the *PNPLA3* polymorphism and a lower risk of competing cardiovascular mortality,[52] both of which may play a role in this strong association. In a recent study by Cherubini et al. it is clearly highlighted that there is an interaction between female sex and the rs738409 variant on all liver damage outcomes, resulting in a larger relative risk in women compared with men.[53] The same study highlights a functional interaction between oestrogen-α receptor and the *PNPLA3* rs738409 variant as the cause of this preferential association. These studies suggest important avenues for refinement towards precision medicine based on the *PNPLA3* genotype in our opinion.

4 | RISK STRATIFICATION FOR HEPATOCELLULAR CARCINOMA AND DECOMPENSATION IN CIRRHOSIS

Another potential use of the *PNPLA3* genotype in clinical practice is risk stratification in patients with advanced liver disease including cirrhosis. While the *PNPLA3* risk allele has been shown to promote HCC in the general population, these associations could have been mediated by its effects on fibrosis.[31,35] We believe that the more relevant question is whether it is associated with risk of outcomes in an at-risk population. The specific outcomes most of interest are HCC and hepatic decompensation. The key risk groups are cirrhosis and at-risk chronic hepatitis B; however, because of a paucity of data on longitudinal outcomes in hepatitis B,[54,55] we will focus on cirrhosis for the rest of this discussion (Table 2).

4.1 | Effects on hepatic decompensation

PNPLA3-rs738409-G has been postulated to promote endothelial activation and procoagulant phenotype by activation of hepatic stellate cells, resulting in more rapid progression of portal hypertension.[63] Associations between the *PNPLA3* genotype and portal hypertensive complications of ascites, hepatic encephalopathy, or variceal bleed have been assessed in several case–control and longitudinal cohort studies. We discuss the literature based on disease aetiology below.

4.1.1 | MASLD

One Austrian study in patients with MASLD with confirmed portal hypertension on manometry found increased mortality in *PNPLA3*-rs738409-GG individuals and higher risk of hepatic decompensation, liver-related mortality, and overall mortality in the SLD population (either MASLD or ALD; $n = 141$).[58] This association remained significant in those with clinically significant portal hypertension (gradient ≥10 mmHg). In a subgroup analysis of a case–control study from Japan, in 106 patients with MASLD-related cirrhosis, *PNPLA3* was significantly associated with hepatic decompensation.[59] A retrospective United States study of 732 patients in contrast reported no association between *PNPLA3*

TABLE 2 Selected studies associating *PNPLA3* genotype with clinical outcomes in patients with cirrhosis.

Study	Study type	N/Aetiology	Country	Outcome(s)	Results
Guyot et al.[56]	Prospective, multicenter	*N* = 532: 48% alcohol, 52% HCV	France	HCC, liver-overall death	HCV: no association with HCC, death, or sustained virologic response Alcohol: rs738409-GG associated with adjusted HR 1.9 (1.31–2.80) for HCC. No association with mortality
Trepo et al.[19]	Meta-analysis	*N* = 2503 (55% alcohol, 38% HCV)	Italy, Germany, Belgium, France	HCC	Significant association between *PNPLA3*-rs738409-G allele: -Overall: per-allele OR 1.77 (1.42–2.19) -Alcohol: per-allele OR 2.20 (1.80–2.67) -HCV: per-allele OR 1.55 (1.03–2.34)
Friedrich et al.[57]	Retrospective analysis of prospectively-collected data, multicenter	*N* = 421: 27% PSC, 25% alcohol, 23% viral. All transplant listed	Germany	HCC, decompensation	HCC: per-allele OR 1.41 (1.03–2.70) overall and 2.40 [1.29–4.46] in alcohol-related cirrhosis. No significant association in HCV cirrhosis. G allele carriers had earlier onset of ascites (12.7 vs. 18.3 months) and hepatic encephalopathy (17.7 vs. 38.1 months) versus non-carriers; no difference in spontaneous bacterial peritonitis or hepatorenal syndrome
Mandorfer et al.[58]	Retrospective analysis of prospectively-collected data, single center	*N* = 372: 62% viral, 28% alcohol, 10% MASLD. All had portal hypertension (HVPG ≥6 mmHg)	Austria	Transplant-free mortality HCC Decompensation Liver-related mortality	GG (vs. CC/CG) genotype was associated with: -No significant difference in HCC incidence: 8% (3–17%) versus 4% (2–7%). -Increased risk of overall mortality: sHR 2.2 (1.2–4.0) -Increased risk of decompensation (sHR 2.1 [1.1–4.0])
Shao et al.[59]	Retrospective, multicenter	*N* = 400: 39% viral, 26% MASLD, 25% alcohol	Japan	Decompensation	GG (vs. CC/CG) genotype was associated with odds ratio of 5.4 (2.3–12.6) for decompensation
Nahon et al.[60]	Prospective, multicenter	*N* = 1145: 58% HCV, 42% alcohol	France	HCC, non-HCC liver-related mortality	G allele carriers had higher HCC incidence at 5 years than noncarriers (11.3% vs. 6.2%). No difference in non-HCC liver-related mortality
Thrift et al.[61]	Prospective, multicenter	*N* = 1911: 40% HCV, 31% MASLD, 17% alcohol	United States	HCC	CG/GG genotype (vs. CC) associated with HR 1.62 (1.08–2.45). Significant interactions with heavy alcohol use and obesity
Urias et al.[62]	Retrospective, single center	*N* = 732: 56% MASLD or cryptogenic, 18% alcohol, 16% viral	United States	HCC, decompensation	HCC: GG genotype (vs. CC/CG) associated with HR 2.42 (1.40–4.17). Decompensation: no association

Note: Effects of *PNPLA3* genotype are reported either as rs738409 genotype (i.e. CC, CG, or GG alleles) or per G allele.

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; HVPG, hepatic venous-portal gradient; MASLD, metabolic dysfunction associated steatotic liver disease; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; sHR, subhazard ratio.

genotype and incidence of hepatic decompensation[62]; while this cohort included multiple causes of liver disease, 56% of participants had MASLD and >50% of patients regardless of aetiology had obesity or type 2 diabetes, implying most of the rest had at least a component of SLD.

4.1.2 | Alcohol-related liver disease

Another retrospective analysis of 421 patients from Germany with cirrhosis from multiple etiologies found that the *PNPLA3* genotype was associated with shorter time to ascites and hepatic encephalopathy in the subset of patients with ALD ($n=105$).[57] The Japanese study cited above noted no difference in hepatic decompensation by *PNPLA3* genotype among patients with alcohol-related liver disease ($n=104$).[59]

4.1.3 | Viral hepatitis

The Austrian study detailed above found no significant associations between *PNPLA3* genotype and hepatic decompensation in patients with viral cirrhosis ($n=231$).[58] Similarly, in the Japanese study above, in patients with viral hepatitis ($n=157$), there was no significant association between the *PNPLA3* genotype and the presence of hepatic decompensation.[59]

4.1.4 | Other or mixed etiologies

In the Japanese study detailed above, there was an increased risk of decompensation among patients with primary biliary cholangitis or autoimmune hepatitis-related cirrhosis, but the interpretation was limited by the small cohort size ($n=33$).[59]

In all, these studies reported that *PNPLA3* genotype is associated with risk of hepatic decompensation. This effect seems to be primarily in patients with MASLD or ALD, with little to no data suggesting association between *PNPLA3* genotype and decompensation in viral cirrhosis, and too few data in patients with other etiologies to make firm conclusions. However, these studies were all small with the largest study including just over 700 participants. In addition, to our knowledge, all studies showing associations between *PNPLA3* genotype and decompensation have been retrospective. Further prospective studies based on disease aetiology are required before this association can be confirmed.

4.2 | Effects on hepatocellular carcinoma

4.2.1 | Alcohol-related liver disease

In one early prospective study from France, Guyot et al. assessed the impact of the *PNPLA3* genotype in 279 patients with alcohol-related cirrhosis.[56] In the ALD cohort, the *PNPLA3* risk allele was associated with HCC (though not overall mortality).[56] The associations between *PNPLA3* genotypes remained significant after adjustment for key risk factors including persistent alcohol intake, Child-Pugh score, age, sex, T2DM, and platelet count. The authors developed and internally validated a predictive model for HCC risk in alcohol-related cirrhosis that included age, sex, body mass index, and *PNPLA3*-rs738409-GG genotype. This score divided patients into three risk categories with 6-year HCC incidence of 3.4%, 12.2%, and 51.7% in low, intermediate, and high-risk groups, respectively. However, this model was not externally validated and the authors did not report how much *PNPLA3* specifically contributed to the model compared to the other risk factors. The incidence of hepatic decompensation based on the *PNPLA3* genotype was not reported, but there was a borderline significant association of higher baseline prevalence of hepatic encephalopathy based on rs738409-G carriage.

4.2.2 | Viral hepatitis

Guyot et al also evaluated the *PNPLA3* genotype in 253 patients with HCV cirrhosis; in this population, there was no association between the *PNPLA3* genotype and HCC or mortality.[56] Of note, this study was conducted before the widespread availability of direct-acting antiviral therapy for HCV, and 75% of HCV patients were still viremic by the end of the study.

4.2.3 | Combined aetiology

The authors of the Guyot et al study then assessed further the impact of *PNPLA3* genotype in two prospective French and Belgian cohorts, one with cured HCV cirrhosis[64] and another with alcohol-related cirrhosis,[65] including 1145 patients in total, with 86 HCC events.[60] While *PNPLA3*-rs738409-G allele was not significantly associated with HCC occurrence in either cohort alone, it was associated in the overall cohort. They also generated two PRSs incorporating *PNPLA3* genotype and found that these scores were associated with incidence of HCC.[60] Both PRSs were significantly associated with HCC incidence even after adjustment for two clinical risk scores for HCC [age-male-albumin-bilirubin-platelets score (aMAP) and an internally derived score]. However, the incremental benefit of incorporating genetics along with the clinical scores was modest, with C-statistic .77 for both clinical models alone versus .78–79 for clinical models with PRSs. Another prospective study from the United States of 1911 patients with cirrhosis, of whom 116 developed HCC during follow-up, *PNPLA3*-rs738409-G carriers had higher risk of HCC and this effect was greater in patients with heavy alcohol intake, obesity, or viral hepatitis.[61] The authors compared models with versus without *PNPLA3* genotype in conjunction with a recently-developed model incorporating several parameters including AFP.[66,67] The C-statistic for 1-year HCC prediction increased from .78 to .83 after adding *PNPLA3* genotype.

Retrospective data also exist to suggest an association between the *PNPLA3* genotype and HCC risk among patients with cirrhosis. Several case–control studies have also demonstrated higher odds of HCC among people with cirrhosis who carried versus who did not carry *PNPLA3* risk alleles.[16,19] Two retrospective studies from Germany and the US, respectively, of 421 and 732 patients with cirrhosis from diverse etiologies of liver disease found that the *PNPLA3* rs738409-GG genotype was associated with a higher incidence of HCC.[57,62] The US study also found that these differences were consistent across disease aetiology and aMAP scores, though they seemed to be greater in patients with steatotic liver disease.

In sum, the literature on the *PNPLA3* genotype suggests that rs738409-G carriage is associated with risk of HCC but whether it promotes hepatic decompensation is less consistent with small cohort sizes. Associations between *PNPLA3* and both decompensation and HCC appear to be more significant in patients with steatotic liver disease.

5 | CONCLUSIONS

Multiple studies have associated the *PNPLA3* genotype with clinical outcomes of liver-related death and/or major adverse liver outcomes in cohorts ranging from the general population to those with advanced fibrosis/cirrhosis. In our opinion, however, the clinical applicability of the *PNPLA3* genotype will require that genotypic data adds incremental information to widely available clinical tools. Here, the data are more limited. To our knowledge, no studies have reported whether the *PNPLA3* genotype can aid with the diagnosis of MASH or fibrotic MASH beyond VCTE or MRE-derived scores. In non-cirrhotic populations, we believe that the *PNPLA3* genotype may help stratify risk beyond simple non-invasive tests in patients with a relatively high pre-test probability of having significant fibrosis based on either non-invasive tests (e.g. FIB4) or demographics (e.g. T2DM). In cirrhotic populations, the literature on *PNPLA3* and hepatic decompensation has yielded mixed results, but there is a clear association between *PNPLA3* genotype and HCC incidence, especially in those with steatotic liver disease. However, whether the *PNPLA3* genotype meaningfully improves upon HCC risk scores such as aMAP in people with cirrhosis is less well-established.

AUTHOR CONTRIBUTIONS

Vincent Chen: drafting and critical review of the manuscript. Umberto Vespasiani-Gentilucci: drafting and critical review of the manuscript.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

Vincent Chen received grants from AstraZeneca, KOWA, and Ipsen, paid to his institution. Umberto Vespasiani-Gentilucci received grants from AstraZeneca, Advanz Pharma, Ipsen, and Diasorin.

DATA AVAILABILITY STATEMENT

Not applicable as no original data were generated for this manuscript.

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How to cite this article: Chen VL, Vespasiani-Gentilucci U. Integrating *PNPLA3* into clinical risk prediction. *Liver Int*. 2025;45:e16103. doi:10.1111/liv.16103