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The rs72613567:TA polymorphism in *HSD17B13* is associated with survival benefit after development of hepatocellular carcinoma

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Summary

Background: The influence of genetic factors on survival following a diagnosis of hepatocellular carcinoma (HCC) remains unclear.

Aim: To assess whether genetic polymorphisms influencing the susceptibility to develop HCC are also associated with HCC prognosis.

Methods: We included United Kingdom Biobank (UKB) participants diagnosed with HCC after study enrolment. The primary outcome was all-cause mortality. Patients were followed from the date of HCC diagnosis to death or the registry completion date. Five HCC susceptibility loci were investigated: rs738409 (*PNPLA3*), rs58542926 (*TM6SF2*); rs72613567 (*HSD17B13*); rs2242652 (*TERT*) and rs708113 (*WNT3A*). The associations between these genetic variants and HCC mortality risk were assessed using Cox regression, adjusted for age, sex, ethnicity, aetiology, severity of the underlying liver disease and receipt of curative HCC treatment.

Results: The final sample included 439 patients; 74% had either non-alcoholic fatty liver disease or alcohol-related liver disease. There were 321 deaths during a mean follow-up of 1.9 years per participant. Kaplan–Meier survival estimates at 1, 3 and 5 years were 53.2%, 31.2% and 22.6% respectively.

In multivariate analysis, rs72613567:TA (*HSD17B13*) was the only genetic susceptibility variant significantly associated with all-cause mortality risk (aHR: 0.74; 95% CI: 0.61–0.90; $p = 0.003$). Other associated factors were Baveno stage 3–4 (aHR: 1.65; 95% CI: 1.05–2.59; $p = 0.03$) and HCC treatment with curative intent (aHR: 0.25; 95% CI: 0.17–0.37; $p < 0.001$).

Conclusions: The rs72613567:TA polymorphism in *HSD17B13* is not only associated with a reduction in the risk of developing HCC but with a survival benefit in HCC once established. Therapeutic inhibition of *HSD17B13* may augment survival in individuals with HCC.

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, responsible for ~800,000 deaths every year world-wide.[1,2] Five-year survival after a diagnosis of HCC < 20%, which is in stark contrast to other types of cancer, for example, prostate cancer, where 5-year net survival exceeds 90%.[3–5] Improving HCC prognosis is therefore a key priority. Early diagnosis of HCC at an incipient stage—that is, when the tumour is small and amenable to curative therapies—is the most critical predictor of 5-year survival.[2,4] However, other patient factors are likely to contribute to HCC survival and identifying these could support the development of risk-stratification tools.

To date, genetic studies have focused on identifying loci associated with the susceptibility to develop HCC[6–10]; five main HCC susceptibility loci have been identified thus far:

- rs738409 in Patatin Like Phospholipase Domain Containing 3 (*PNPLA3*)[6–8]
- rs58542926 in Transmembrane 6 Superfamily Member 2 (*TM6SF2*)[6]
- rs72613567 in Hydroxysteroid 17-Beta Dehydrogenase 13 (*HSD17B13*)[9]
- rs2242652 in Telomerase Reverse Transcriptase (*TERT*)[7]
- rs708113 in the of region of Wingless-Type MMTV Integration Site Family, Member 3A (*WNT3A*)[8]

In certain cancers, for example, renal,[10] prostate[11] and breast,[12] genetic factors associated with the susceptibility to cancer development have also been shown to influence outcomes. However, little is known about possible genetic influence on the outcome of HCC. The aim of this study was to assess whether the genetic risk factors known to influence HCC development also influence disease outcome.

2 | METHODS

2.1 | Data source

The United Kingdom Biobank (UKB) is a community cohort study which has collected and continues to collect extensive environmental, lifestyle and genetic data from 502,492 UK residents. Some 9 million persons aged 40–69 years living within 25 miles of one of 22 UKB assessment centres were invited to take part in the study. Those accepting were enrolled between May 2006 and July 2010; they completed comprehensive health questionnaire and donated biological samples including DNA.[13] Follow-up data on subsequent health outcome events are supplied through record linkage to UK mortality, hospital and cancer registries.[14] Since study enrolment, more than 25,000 participants have been diagnosed with a malignancy.

2.2 | Study population

This study included all participants with an incident HCC presentation following UKB enrolment. Incident HCC was defined as the first record of an ICD:C22.0 code in either (a) an in-patient hospital admission record; or (b) a cancer registration record; or (c) the mortality register. Only ICD10:C22.0 codes present in the main/underlying diagnostic or cause of death position were used to define HCC. The earliest HCC diagnosis/presentation date across these three registers was assumed to be the HCC incidence date.

Patients were excluded if they had incomplete information for any of the 5 HCC genetic susceptibility loci considered in this study. Participants were also excluded if they were a first or second-degree relative of another participants (inferred via a kinship coefficient >=0.1).

UKB participants without an incident HCC diagnosis served as controls to confirm each variant's association with HCC susceptibility.

2.3 | Primary outcome event

The primary outcome event was all-cause mortality consistent with how cancer prognosis is defined in the wider literature.[15]

2.4 | HCC susceptibility loci

Genotype status of five HCC genetic susceptibility loci was ascertained from version 3 of the UKB imputed genetic dataset (downloaded May 2019) viz:

- rs738409:G in *PNPLA3*: associated with an *increased* HCC risk[6–8]
- rs58542926:T in *TM6SF2*: associated with an *increased* HCC risk[6]
- rs72613567:TA in *HSD17B13*: associated with a *reduced* HCC risk[9]
- rs242652:A in *TERT*: associated with a *reduced* HCC risk[7] and
- rs708113:T near *WNT3A*: associated with a *reduced* HCC risk[8]

2.5 | Non-genetic covariates

Liver disease aetiology was identified using a hierarchical definition of: (#a) viral hepatitis, (#b) autoimmune liver disease in the absence of (#a; #c) alcohol-related liver disease (ArLD) in the absence of (#a-#b; #d) non-alcoholic fatty liver disease (NAFLD) in the absence of (#a–#c; and #e) other/unknown in the absence of (#a–#d). Risk factors for these aetiologies were discerned through a combination of hospital admissions and/or information reported during the UKB enrolment interview (Table S1).

The presence and severity of cirrhosis were defined using hospital admission data prior to HCC presentation. Specifically, the algorithm developed by Driver et al,[16] which uses hospital admission episodes in the past 5 years to group individuals with HCC

into distinct cirrhosis severity groups was adopted. These severity groups were as follows: (a) no cirrhosis; (b) cirrhosis without varices or ascites; (c) cirrhosis with non-bleeding varices; (d) cirrhosis with ascites; (e) cirrhosis with bleeding varices.

Episodes of HCC treatment with curative intent were identified from surgical OPCS4 hospital procedure codes appearing in combination with an ICD10:C22.0 code. OPCS4 codes for ablation (J124; J127; J125; J126; J033; Y134; J083) resection (J023; J021; J022; J024; J027) and liver transplantation (J011; J015) were included. These specific codes were identified through a two-stage process: (a) extracting all hospital admissions for HCC present in the UKB cohort (N = 1134); and then (b) reviewing and categorising all OPCS4 codes included within these 1134 hospital admissions according to whether they refer to instances of curative treatment or not, as defined by the relevant EASL clinical guidelines.[2] (Table S2). Ethnicity was defined based on whether participants were of white British ancestry or not, using UKB field ID:22006. Finally, data on FIB-4, measured at the time of UKB enrolment were also extracted.

2.6 | Statistical analyses

First, the minor allele frequencies for the selected variants in the final HCC sample were compared with those in non-HCC controls to confirm associations with HCC susceptibility. p-values were generated from a logistic regression model with adjustment for age at UKB enrolment and sex.

Second, Cox regression was used to determine independent associations between each genetic variable and mortality risk following an HCC diagnosis. Follow-up time began at the date of incident HCC and ended at the date of death or 31 October 2021, which is the latest date the UKB mortality data were available at the time of this analysis. Genetic associations were calculated under both an additive and genotypic model. A Bonferroni-corrected significance threshold of $p < 0.01$ (i.e. 0.05/5) was used to judge statistical significance for genetic associations to account for multiple testing. All models included adjustment for age at HCC diagnosis, sex, ethnicity, aetiology and severity of the underlying liver disease, receipt of curative HCC treatment and the first 10 principal components of genetic ancestry.

Receipt of HCC curative therapy was incorporated as a time-dependent variable—thereby accommodating changes in treatment status during the course of follow-up and avoiding immortal time bias.[17] The proportional hazards assumption was verified for all models using the global Schoenfeld residual test.

2.7 | Sensitivity analyses

Several sensitivity analyses were performed to assess the robustness of, or further interrogate, the findings. First, the analysis was restricted to patients with ArLD and NAFLD, as genetic susceptibility to HCC may vary by aetiology, particularly in relation to chronic viral hepatitis.[18,19] Second, the main analysis was repeated for liver-related mortality, defined as a death from liver cancer (ICD10:C22) or chronic liver disease (ICD10: K70-K77 codes) recorded in any position on the death certification. Third, the potential interaction between rs72613567 in HSD17B13 and rs738409 in PNPLA3 with assessed in respect to HCC survival. This was prompted by previous evidence of epistasis between these polymorphisms.[20] Fourth, associations were also adjusted for the FIB-4 score measured at UKB enrolment. Fifth, associations were stratified by cirrhosis status at the time of HCC diagnosis (i.e. Baveno group 0 vs. 1–4). Finally, the analysis was restricted to individuals of White British ancestry, defined using the UKB field ID: 22006.

3 | RESULTS

3.1 | Derivation of final sample

A total of 456 UKB participants met our inclusion criteria; 17 participants without available genetic data were excluded. Thus, our final sample comprised of 439 participants with incident HCC.

A total of 467,673 UKB participants without evidence of an incident HCC, during the time frame of the study, served as controls for disease susceptibility.

3.2 | Characteristics of final sample

The majority of the 439 participants were male (78%) and aged >70 years at diagnosis (mean age: 69.2) (Table 1). NAFLD was the most common underlying liver disease (41%) followed by alcohol-related liver disease (33%) and viral hepatitis (11%). Most individuals (55%) did not have a previously recorded hospital admission with cirrhosis. Only one-fifth (20%) received curative treatment for HCC during follow-up. The mean and median FIB-4 score at UKB enrolment were 2.8 and 2.1 respectively. However, FIB-4 values were measured, on average, 7.4 years before HCC diagnosis (Figure S1).

The minor allele frequencies of the genetic susceptibility variants in the HCC participants ranged from 14.9% (rs58542926 in TM6SF2) to 39.4% (rs708113 in WNT3A), in line with previously published data.[6–9]

3.3 | HCC susceptibility

With the exception of rs708113 near WNT3A, all of the selected variants were significantly associated with HCC susceptibility although with differences in the directionality of the effect (Figure 1A and Table S3). Thus, rs738409 in PNPLA3 and rs58542926 in TM6SF2 were associated with an increased risk for developing HCC, while rs72613567 in HSD17B13 and rs242652 in TERT were associated with a reduced (protective) risk.

TABLE 1 Demographic, clinical and genotypic data in the 439 UKB participants with HCC.

Characteristic	
Demographic factors	
Mean age, years (±1 SD)	69.2 (±6.9)
Male gender	340 (77.5%)
White British ancestry	370 (84.3)
Clinical factors	
HCC aetiology	
NAFLD	179 (40.8%)
Alcohol	145 (33.0%)
Viral hepatitis	49 (11.2%)
Autoimmune	19 (4.3%)
Other/unknown	47 (10.7%)
Cirrhosis stage	
No cirrhosis	242 (55.1%)
Baveno stage 1	107 (24.4%)
Baveno stage 2	61 (13.9%)
Baveno stage 3/4	29 (6.6%)
Genetic factors	
HCC curative treatment	87 (19.8%)
rs738409 (*PNPLA3*)	
CC	217 (49.4)
CG	167 (38.0)
GG	55 (12.5)
G Allele frequency	31.5%
rs58542926 (*TM6SF2*)	
CC	325 (74.0)
CT	97 (22.1)
TT	17 (3.9)
T allele frequency	14.9%
rs72613567 (*HSD17B13*)	
TT	273 (62.2)
T TA	140 (31.9)
TA TA	26 (5.9)
TA allele frequency	21.9%
rs2242652 (*TERT*)	
GG	312 (71.1)
GA	114 (26.0)
AA	13 (3.0)
A allele frequency	15.9%
rs708113 (*WNT3A*)	
AA	159 (36.2)
AT	214 (48.8)
TT	66 (15.0)
T allele frequency	39.4%

Note: With the exception of allele frequencies for genetic factors, all cells indicate the number of patients, followed by column percentage in parentheses.

3.4 | Post-HCC mortality

The study cohort was followed for 840 person-years after HCC diagnosis. The mean and median follow-up time per participant was 1.91 and 0.95 years respectively (Table S4). In total, 321 deaths were observed. The Kaplan–Meier survival estimate at 1, 3 and 5 years were 53.2% (95% CI: 48.4–57.8); 31.2% (95% CI: 26.7–35.9) and 22.6% (95% CI:18.3–27.2) respectively (Figure 1B). The median survival time was 1.30 years (95% CI: 0.89–1.59). Of the 321 deaths observed, 295 (92%) were categorised as liver-related deaths, as previously defined (Table S4).

3.5 | Factors associated with HCC survival

3.5.1 | Genetic factors

In multivariate analysis, rs72613567 in *HSD7B13* was significantly associated with better overall survival following HCC diagnosis. Specifically, individuals carrying the TA allele had a lower mortality risk than carriers of the T allele (aHR:0.74; 95% CI:0.61–0.90; $p = 0.003$) (Figure 1C; Table 2). The genotypic association was aHR:0.80 ($p = 0.09$) for TA heterozygotes; and 0.50 ($p = 0.01$) for TA homozygotes all relative to the TT genotype (Figure S2).

The association with rs72613567 in *HSD7B13* and all-cause mortality was also significant in the subgroup of participants with NAFLD and alcohol-related liver disease (aHR: 0.68; 95% CI: 0.54–0.86; $p = 0.001$) (Table 3). The rs72613567 variant was also significantly associated with liver-related mortality (aHR: 0.74; 95% CI: 0.60–0.91; $p = 0.004$) (Figure S3). There was no indication of a strong interaction with rs738409 in *PNPLA3*, nor did the association attenuate with adjustment for FIB-4 scores. The association between rs72613567 in *HSD7B13* and all-cause mortality was greater in participants who did not have cirrhosis (HR:0.67; 95% CI: 0.51–0.88; $p = 0.004$) compared with those who did (HR: 0.85; 95% CI: 0.62–1.16; $p = 0.31$); however, the difference was not statistically significant, indicated by the overlapping confidence intervals (Table 3).

In contrast, rs738409 (*PNPLA3*); rs58542926 (*TM6SF2*); rs2242652 (*TERT*) and rs708113 (*WNT3A*) were not significantly associated with either all-cause or liver-related mortality (Figure 1C, Figures S2 and S3).

3.5.2 | Non-genetic factors

The strongest predictor of all-cause mortality risk was receiving curative HCC treatment; this was associated with >70% reduction in the HCC mortality hazard (aHR: 0.25; 95% CI: 0.17–0.37; $p < 0.001$) (Table 2). Advanced cirrhosis (i.e. Baveno stage 3/4) was associated with a higher risk of all-cause mortality compared to non-cirrhosis (aHR: 1.65; 95% CI: 1.05–2.59; $p = 0.03$) (Table 2). Otherwise, no significant associations were observed in relation to age, sex or liver disease aetiology.
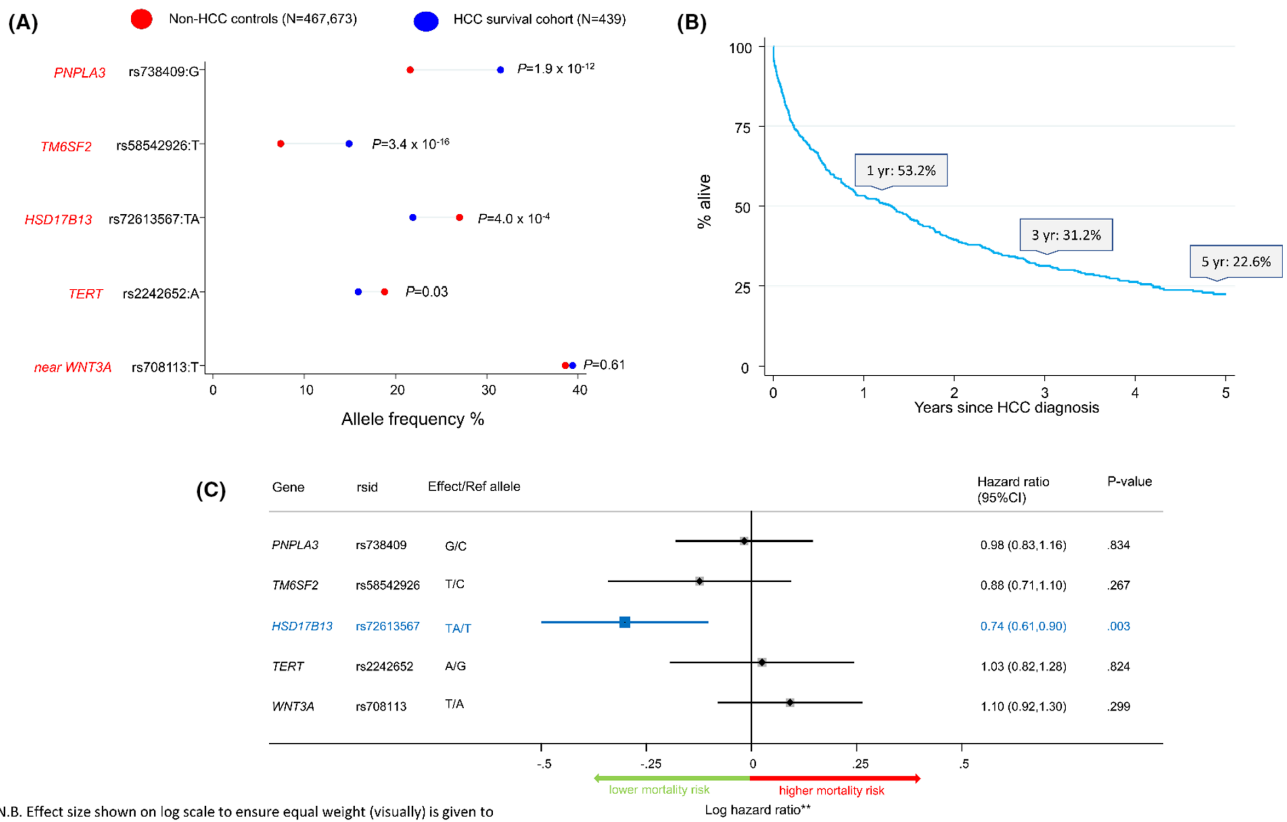
FIGURE 1 Influence of genetic variants on HCC susceptibility and prognosis. Panel (A) Allele frequency in study cohort versus non-HCC controls. (B) Kaplan–Meier survival proportion following HCC diagnosis. (C) Adjusted association between genetic polymorphisms and post-HCC mortality risk.

4 | DISCUSSION

The aim of this study was to assess if genetic polymorphisms that are known to influence susceptibility to HCC, may also be associated with HCC prognosis. The data show that survival following HCC diagnosis is associated with the *HSD17B13*: rs72613567 genotype. The directionality of the association with HCC survival was consistent with its effect on HCC susceptibility. Thus, individuals carrying rs72613567:TA are less likely to develop HCC[9]; those who do develop an HCC appear to have a survival advantage compared with carriers of rs72613567:T. In contrast, there was no convincing evidence of an association between HCC prognosis and susceptibility loci in *PNPLA3*, *TM6SF2*, *TERT* or *WNT3A*. Likewise, there was no association between HCC prognosis and age, sex, ethnicity or liver disease aetiology, although there was a significant negative association with disease severity. This study also underscores the appreciable influence that curative-intent HCC treatments have on prognosis. Indeed, the mortality risk was 75% lower in individuals who received curative therapy compared to those who did not. Unfortunately, only one in five HCC participants in this cohort received curative therapies, which is consistent with estimates from elsewhere.[21] This likely reflects that fact that the majority of participants with HCC in this cohort, as is generally the case, were first diagnosed when they already have intermediate/advanced disease

when treatment with curative intent is no longer possible.[2] This clearly indicates that early HCC detection is imperative to improve net survival.

The role of HSD17B13 in human physiology and the molecular mechanism responsible for its hepatoprotective effects are largely unknown. The hepatoprotective association may relate to the role of the protein product HSD17B13 as a retinol dehydrogenase (RDH), which is highly expressed in the liver.[22] The rs72613567:TA allele is a loss of function variant, leading to diminished RDH activity. Amangurbanova et al,[23] have proposed that reduced RDH activity results in increased vitamin A storage in hepatic stellate cells, which in turn reduces inflammation, fibrogenesis and hepatic stellate cell activation. Interest has been shown in the possibility that HSD17B13 inhibition may provide an attractive drug target.[24] This is supported by the fact that: (i) the hepatoprotective effect of the rs72613567 variant in *HSD17B13* is relatively consistent across ethnic groups and broadly across liver disease aetiologies and, (ii) HSD17B13 deficiency caused by homozygous carriage of the rs72613567 variant does not appear to cause any direct adverse events in humans. The results of the present study imply that HSD17B13 may be a therapeutic target for HCC, and that HSD17B13 inhibitors—which are being evaluated in clinical trials as a treatment for NAFLD[25]—may favourably influence HCC prognosis. However, the biological role

TABLE 2 Demographic, clinical and genetic risk factors in UKB participants with HCC associated with all-cause mortality.

Characteristic	Univariate		Multivariate*	
	Hazard ratio	p	Adjusted hazard ratio	p
rs738409:G (*PNPLA3*)	0.95 (0.81–1.11)	0.50	0.98 (0.83–1.16)	0.83
rs58542926:T (*TM6SF2*)	0.93 (0.75–1.14)	0.47	0.88 (0.71–1.10)	0.27
rs72613567:TA (*HSD17B13*)	**0.77 (0.64–0.93)**	**0.006**	**0.74 (0.61–0.90)**	**0.003**
rs2242652:A (*TERT*)	0.90 (0.72–1.11)	0.32	1.03 (0.82–1.28)	0.82
rs708113:T (*WNT3A*)	1.03 (0.88–1.22)	0.68	1.10 (0.92–1.30)	0.30
Age, per 10 years increase	1.13 (0.96–1.34)	0.14	1.10 (0.92–1.33)	0.30
Sex				
Female	REF (1.00)	–	REF (1.00)	–
Male	1.14 (0.87–1.49)	0.34	1.09 (0.79–1.51)	0.59
White British ancestry				
Yes	REF (1.00)	–	REF (1.00)	–
No	1.20 (0.89–1.64)	0.24	0.67 (0.42–1.08)	0.10
HCC aetiology				
NAFLD	REF (1.00)	–	REF (1.00)	–
Alcohol	1.22 (0.95–1.57)	0.12	1.19 (0.91–1.55)	0.21
Viral hepatitis	0.69 (0.47–1.01)	0.06	0.85 (0.53–1.35)	0.48
Autoimmune	0.80 (0.44–1.44)	0.45	0.77 (0.41–1.44)	0.41
Other/unknown	1.02 (0.70–1.49)	0.93	1.22 (0.79–1.91)	0.37
Cirrhosis severity				
No cirrhosis	REF (1.00)	–	REF (1.00)	–
Baveno stage 1	0.90 (0.69–1.18)	0.45	0.99 (0.74–1.33)	0.97
Baveno stage 2	0.97 (0.70–1.35)	0.84	1.09 (0.75–1.57)	0.66
Baveno stage 3/4	**2.11 (1.34–3.31)**	**0.001**	1.65 (1.05–2.59)	0.03
HCC curative treatment				
No	REF (1.00)	–	REF (1.00)	–
Yes	**0.25 (0.17–0.36)**	**<0.001**	**0.25 (0.17–0.37)**	**<0.001**

*Multivariate model also included adjustment for the first 10 principal components of genetic ancestry, however, the coefficients for these terms are omitted from this table; emboldened variables are independently associated with mortality risk at $p < 0.01$.

of HSD17B13 is poorly understood particularly its role in hepatic lipid metabolism. In addition, the interplay between HSD17B13 and PNPLA3 is an important confounder, particularly as PNPLA3 may also be a target for therapeutic inhibition.[26] Thus, further clarification of the physiological role of HSD17B13 and a better understanding of the genetic basis of its hepatoprotective effects are needed before its value as a potential therapeutic target can be embraced with certainty.

Previous studies have shown unequivocally that rs72613567:TA in *HSD17B13* protects against the development of cirrhosis, HCC and liver mortality[7–9,27,28]—yet opinion is divided on the prognostic significance of this variant for patients with advanced liver disease.[29,30] The present study looked specifically at the possible roles played by known genetic risk loci for the development of HCC on survival following diagnosis. To our knowledge, there are no other studies which have examined the prognostic relevance of the rs72613567 polymorphism in this way. In an earlier study,

Valenti and colleagues reported that carriage of the rs738409:G allele (*PNPLA3*) was associated with inferior survival following HCC diagnosis in a cohort of HCC patients from Northern Italy.[31] Nevertheless, this association was only observed within a small subgroup of patients with ALD and NAFLD ($n = 101$; HR = 1.87; $p = 0.02$), and not in those with other liver disease aetiologies ($n = 255$; HR = 1.12; $p = 0.55$). In contrast, our data do not support this finding, suggesting instead that rs738409 has a neutral effect on HCC prognosis.

This study has numerous limitations. First, for lack of a better alternative, the presence of cirrhosis was established from hospital admission episodes occurring prior to HCC diagnosis using an algorithm proposed by Driver et al.[16] Using this approach, only 45% of participants had been hospitalised for cirrhosis before presentation with HCC. However, this is likely a significant underestimate as cirrhosis is often asymptomatic and does not typically lead to an inpatient hospital admission until disease decompensation.

TABLE 3 Association between rs72613567 in *HSD17B13* and mortality risk in sensitivity analyses.

Sensitivity analysis	Description	Sample size	No. of events	Effect/ref allele	aHR (95% CI)	*p*-value
Base-case analysis		**439**	**312**	**TA/T**	**0.74 (0.61–0.90)**	**0.003**
1. Aetiology	Alcohol and NAFLD	324	242	TA/T	0.68 (0.54–0.86)	0.001
2. Cause of death	Liver-related mortality	439	295	TA/T	0.74 (0.60–0.9)	0.004
3. PNPLA3 interaction	rs738409 CC genotype	217	162	TA/T	0.75 (0.54–1.02)	0.07
	rs738409 CG or GG genotype	222	159	TA/T	0.70 (0.53–0.93)	0.012
4. Residual confounding	+ adjustment for FIB-4	412[a]	301	TA/T	0.74 (0.60–0.90)	0.003
5. Cirrhosis severity	No cirrhosis	242	180	TA/T	0.67 (0.51–0.88)	0.004
	Baveno groups 1–4	197	141	TA/T	0.85 (0.62–1.16)	0.31
6. Ethnicity	White British ancestry	370	273	TA/T	0.77 (0.62–0.95)	0.016

Note: All associations adjusted for age; sex; ethnicity; liver disease severity, aetiology, curative HCC treatment and the first 10 principal components of genetic ancestry.

[a]FIB4 missing in 27 individuals.

Driver et al,[16] have suggested including hospital admissions occurring after HCC diagnosis to improve sensitivity, but this could lead to "immortal time bias" in a survival analysis context and so was not employed. Thus, residual confounding by cirrhosis severity is a possibility. In a sensitivity analysis, the association between rs72613567 and mortality did not attenuate with adjustment for FIB-4, a routine marker of fibrosis severity. However, the FIB-4 data were measured 7 years prior to HCC diagnosis on average and hence should be used with caution. Second: the present study cohort may not be generalisable to HCC patients in the United Kingdom as a whole. UKB participants are generally healthier than the general UK population and have lower mortality and cancer incidence rates.[32] Nevertheless, the 5-year survival rates observed in this cohort at 22.6% were very similar to nationally representative estimates from the United Kingdom.[5] Our sample was also heterogeneous in terms of liver disease aetiology, liver disease severity and HCC stage at diagnosis; thus, the associations reported may not be equivalent for all types of patient. However, the sensitivity analyses we performed are an attempt to identify if any major differences exist. Our sample size was also relatively modest comprising of only 439 individuals, which precluded performance of detailed subgroup analyses. Our methods did not include independent validation in an external cohort, which is another key limitation of this study. Further, we had insufficient information to allow HCC classification at diagnosis using Barcelona Clinic Liver Cancer (i.e. BCLC) criteria. However, uptake of curative HCC therapies can be considered a reasonable proxy for early HCC detection.[2] Finally, due to limited statistical power, this study focused on five well-established HCC susceptibility loci that have been robustly replicated across cohorts. The rs28929474 variant in *SERPINA1* was not included because it is rare and it is unlikely that the statistical power would have been insufficient to detect an association with HCC survival, even if one existed. The rs641738 variant in *MBOAT7* and the rs1260326 variant in *GCKR* were also not included because while they are included in some polygenic risk scores for HCC,[33] their independent associations with HCC susceptibility are equivocal.

In conclusion, this study demonstrates that carriage of the rs72613567:TA variant in *HSD17B13* is associated with survival benefit after HCC diagnosis. Further studies are now needed to corroborate this finding and elucidate the therapeutic corollaries.

AUTHOR CONTRIBUTIONS

Hamish Innes: Conceptualization (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); resources (equal); writing – original draft (equal); writing – review and editing (equal). **Marsha Y. Morgan:** Conceptualization (equal); investigation (equal); methodology (equal); resources (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Jochen Hampe:** Conceptualization (equal); investigation (equal); resources (equal); supervision (equal); writing – review and editing (equal). **Felix Stickel:** Conceptualization (equal); investigation (equal); resources (equal); supervision (equal); writing – review and editing (equal). **Stephan Buch:** Conceptualization (equal); investigation (equal); methodology (equal); resources (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors have no personal conflicts of interest to declare.

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REFERENCES

1. Akinyemiju T, Abera DS, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional and national level. JAMA Oncol. 2017;3:1683–91.
2. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69:182–236.
3. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, et al. Global surveillance of trends in cancer survival 2000-2014 (CONCORD-3): analysis of individual records for 37 513025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391:1023–75.
4. Zhang X, El-Serag HB, Thrift AP. Predictors of five-year survival among patients with hepatocellular carcinoma in the United States: an analysis of SEER-Medicare. Cancer Causes Control. 2021;32:317–25.
5. Burton A, Tataru D, Driver RJ, Bird TG, Huws D, Wallace D, et al. Primary liver cancer in the UK: incidence, incidence-based mortality, and survival by subtype, sex and nation. JHEP Rep. 2021;3:100232.
6. Stickel F, Buch S, Nischalke HD, Weiss KH, Gotthardt D, Fischer J, et al. Genetic variants in *PNPLA3* and *TM6SF2* predispose to the development of hepatocellular carcinoma in individuals with alcohol-related cirrhosis. Am J Gastroenterol. 2018;113:1475–83.
7. Buch S, Innes H, Lutz PL, Nischalke HD, Marquardt JU, Fischer J, et al. Genetic variation in *TERT* modifies the risk of hepatocellular carcinoma in alcohol-related cirrhosis: results from a genome-wide case-control study. Gut. 2022;72:381–91. https://doi.org/10.1136/gutjnl-2022-327196
8. 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.
9. Stickel F, Lutz P, Buch S, Nischalke HD, Silva I, Rausch V, et al. Genetic variation in *HSD17B13* reduces the risk of developing cirrhosis and hepatocellular carcinoma in alcohol misusers. Hepatology. 2020;72:88–102.
10. Liu Y, Han X, Yongwei Y, Ding Y, Liu W, Hou X, et al. A genetic polymorphism affects the risk and prognosis of renal cell carcinoma: association with follistatin-like protein 1 expression. Sci Rep. 2016;6:26689.
11. Zhao L, Zhen W, Li C. Association of long-chain non-coding RNA *GAS5* gene polymorphism with prostate cancer risk and prognosis in Chinese Han population. Medicine. 2020;99:e21790.
12. Peterson NB, Beeghly-Fadiel A, Gao YT, Long J, Cai Q, Shu X, et al. Polymorphisms in tissue inhibitors of metalloproteinases-2 and -3 and breast cancer susceptibility and survival. Int J Cancer. 2009;125:844–50.
13. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779.
14. UK Biobank malignant cancer summary report. https://biobank.ndph.ox.ac.uk/~bbdatan/CancerSummaryReport.html. Accessed June 2021.
15. Allemani C, Matsuda T, Carlo VD, Harewood R, Matz M, Niksic M, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37513025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391:1023–75.
16. Driver RJ, Balachandrakumar V, Burton A, Shearer J, Downing A, Cross T, et al. Validation of an algorithm using inpatients electronic health records to determine the presence and severity of cirrhosis in patients with hepatocellular carcinoma in England: an observational study. BMJ Open. 2019;9:e028571.
17. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010;340:B5087.
18. Bianco C, Casirati E, Malvestiti F, Valenti L. Genetic predisposition similarities between NASH and ASH: identification of new therapeutic targets. JHEP Rep. 2021;3:100284.
19. Nischalke HD, Berger C, Luda C, Berg T, Muller T, Grunhage F, et al. The *PNPLA3* rs738409 148M/M genotype is a risk factor for liver cancer in alcoholic cirrhosis but shows no or weak association in hepatitis C cirrhosis. PLoS One. 2011;6(11):e27087.
20. Gellert-Kristensen H, Nordestgaard BG, Tybaerg-Hansen A, Stender S. High risk of fatty liver disease amplifies the alanine transaminase lower effect of a *HSD17B13* variant. Hepatology. 2020;71:56–66.
21. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med. 2014;11:e1001624.
22. 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 nonalcoholic fatty liver disease. Hepatology. 2019;69:1504–19.
23. Amangurbanova M, Huang DQ, Loomba R. Review article: the role of *HSD17B13* on global epidemiology, natural history, pathogenesis and treatment of NAFLD. Aliment Pharmacol Ther. 2023;57:37–51.
24. Romeo S. HSD17B13 as a promising therapeutic target against chronic liver disease. Liver Int. 2020;40:756–7.
25. Mak L, Gane E, Schwabe C, Yoon KT, Heo J, Scott R, et al. A phase I/II study of ARO-HSD, an RNA interference therapeutic, for the treatment of non-alcoholic steatohepatitis. J Hepatol. 2023;4:684–92.
26. Lindén D, Ahnmark A, Pingitore P, Ciociola E, Ahlstedt I, Andreasson A-C, et al. Pnpla3 silencing with antisense oligonucleotides ameliorates nonalcoholic steatohepatitis and fibrosis in Pnpla3 I148M knock-in mice. Mol Metab. 2019;22:49–61.
27. 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;378:1096–1106.
28. Gellert-Kristensen H, Tybjaerg-Hansen A, Nordestgaard BG, Ghouse J, Fuchs A, Kuhl JT, et al. Genetic risk of fatty liver disease and mortality in the general population: a mendelian randomisation study. Liver Int. 2023. https://doi.org/10.1111/liv.15629
29. 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. https://doi.org/10.3390/ijms231911840
30. Scheiner B, Stattermayer AF, Schwabl P, Bucsics T, Paternostro R, Bauer D, et al. *HSD17B13* rs72613567 genotype on hepatic decompensation and mortality in patients with portal hypertension. Liver Int. 2020;40:393–404.
31. Valenti L, Motta BM, Soardo G, Iavarone M, Donati B, Sangiovanni A, et al. PNPLA3 I148M polymorphism, clinical presentation, and survival in patients with hepatocellular carcinoma. PLoS One. 2014;8:e75982.
32. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. Am J Epidemiol. 2017;186:1026–34.

33. Biano C, Jamialahmadi O, Pelusi S, Baselli G, Dongiovanni P, Zanoni I, et al. Non-invasive stratification of hepatocellular risk in non-alcoholic fatty liver using polygenic risk scores. J Hepatol. 2021;74:775–82.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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