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Steatosis-associated genetic variants and survival after hepatocellular carcinoma diagnosis: protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No support.

Review stage at the time of initial registration - Completed but not published.

Conflicts of interest - Francisco Tustumi is the Lead Guest Editor of the Cancer Control Special Collection “Obesity, Metabolic Dysfunction, and Cancer”; the other authors declare no conflicts of interest.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 November 2026 and was last updated on 18 November 2026.

INTRODUCTION

Review question / Objective In adults with hepatocellular carcinoma (HCC), are germline steatosis-associated variants (PNPLA3 rs738409, the primary exposure; TM6SF2 rs58542926; HSD17B13 rs72613567 or its proxy rs6834314; MBOAT7 rs641738; and GCKR rs1260326 or rs780094) associated with overall survival and recurrence after HCC diagnosis, and is the association of PNPLA3 modified by the etiology of liver disease?.

Rationale Germline variants that promote hepatic steatosis are established risk factors for metabolic dysfunction-associated steatotic liver disease (MASLD) and for the development of HCC. Whether they also predict outcomes once HCC is diagnosed is uncertain: individual cohort studies have reported harmful, null, and protective associations, and the only previous meta-analysis of survival after diagnosis included 3 studies of PNPLA3. Clarifying the prognostic value of these variants is relevant to proposals to use genetic and polygenic scores in hepatology and oncology.

Condition being studied Hepatocellular carcinoma of any etiology (metabolic, alcohol-related, viral, or other). The germline variants are assessed as prognostic factors for outcomes after HCC diagnosis, not as risk factors for developing HCC.

METHODS

Search strategy An initial PNPLA3-specific search of bibliographic databases from inception was followed, when the scope was extended to the other variants, by an updated search on November 18, 2026, without date or language limits. PubMed search 1: (HSD17B13[tiab] OR rs72613567[tiab] OR rs6834314[tiab] OR "17-beta hydroxysteroid dehydrogenase 13"[tiab] OR TM6SF2[tiab] OR rs58542926[tiab] OR PNPLA3[tiab] OR

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rs738409[tiab] OR adiponutrin[tiab] OR I148M[tiab]) AND (hepatocellular carcinoma[tiab] OR HCC[tiab] OR "liver cancer"[tiab] OR "Carcinoma, Hepatocellular"[mh]) AND (survival[tiab] OR prognos*[tiab] OR recurren*[tiab] OR mortality[tiab] OR death[tiab] OR outcome*[tiab] OR "hazard ratio"[tiab]). PubMed search 2: (MBOAT7[tiab] OR rs641738[tiab] OR GCKR[tiab] OR rs1260326[tiab] OR rs780094[tiab]) AND (hepatocellular carcinoma[tiab] OR HCC[tiab] OR "liver cancer"[tiab] OR "Carcinoma, Hepatocellular"[mh]) AND (survival[tiab] OR prognos*[tiab] OR recurren*[tiab] OR mortality[tiab] OR death[tiab] OR outcome*[tiab] OR "hazard ratio"[tiab]). Europe PMC (including preprints): (TITLE_ABS:(MBOAT7 OR rs641738 OR GCKR OR rs1260326 OR rs780094 OR HSD17B13 OR rs72613567 OR rs6834314 OR TM6SF2 OR rs58542926 OR PNPLA3 OR rs738409 OR adiponutrin)) AND (TITLE_ABS:("hepatocellular carcinoma" OR HCC OR "liver cancer")) AND (TITLE_ABS:(survival OR prognosis OR prognostic OR recurrence OR "hazard ratio" OR mortality OR death OR outcome OR outcomes)). Reference lists of all full texts and citing articles of included studies were also searched.

Participant or population Adults with HCC confirmed by histology or standard imaging criteria and genotyped for at least 1 of the variants of interest, in any treatment setting, country, or etiology.

Intervention Germline genotype (prognostic factor). PNPLA3 rs738409 GG genotype (recessive model, primary contrast). For the other variants, carriage of the variant allele (TM6SF2 rs58542926 T; HSD17B13 rs72613567 TA or rs6834314 G) or the contrast reported by the studies (eg, MBOAT7 rs641738 TT vs CC+CT; GCKR rs780094 TT vs CC+CT).

Comparator PNPLA3 CC+CG; noncarriers of the variant allele, or the complementary genotype group of the reported contrast, for the other variants.

Study designs to be included Cohort studies (prospective or retrospective) and survival analyses of the HCC cases in case-control studies. Excluded: studies of HCC risk or incidence only, studies of tumor gene expression rather than germline genotype, cross-sectional studies, reviews, editorials, conference abstracts, and animal or in vitro studies.

Eligibility criteria Studies reporting overall survival, recurrence-free survival, or recurrence by genotype, as a hazard ratio (HR) or as data from which an HR can be obtained (genotype-specific HRs, log-rank P values with event counts, or Kaplan-Meier curves). No restrictions on language, publication date, country, treatment, or etiology.

Information sources Bibliographic databases for the initial PNPLA3 search (the protocol planned MEDLINE, Embase, CENTRAL, Web of Science, Scopus, and LILACS); PubMed and Europe PMC, including preprints, for the updated search; and reference lists and citing articles of included studies. Study authors were not contacted.

Main outcome(s) Overall survival after HCC diagnosis, expressed as the HR for death (risk genotype vs comparator) with its 95% CI; adjusted HRs were preferred when both adjusted and unadjusted estimates were reported, and unadjusted estimates were also pooled separately.

Additional outcome(s) Recurrence-free survival or recurrence (HR); cancer-specific survival when reported; and, post hoc, advanced stage at diagnosis and Child-Pugh class B or C by PNPLA3 genotype (odds ratios).

Data management Records were deduplicated by PubMed identifier, DOI, and normalized title and screened in 2 stages (titles and abstracts, then full texts) by 2 independent reviewers, with disagreements resolved by a third reviewer. Two reviewers independently extracted data following CHARMS-PF: country, setting, period, design, sample size, genotype distribution, etiology, stage, treatment, genotyping method, Hardy-Weinberg equilibrium, time origin, follow-up, outcome definitions, adjustment variables, and all survival estimates by genotype. HRs were obtained in a prespecified order: the reported HR; an HR derived from published numbers (combination of genotype-specific HRs based on the method of Hamling et al; conversion of log-rank P values following Tierney et al); and, only when no usable numbers were available, reconstruction of individual patient data from digitized Kaplan-Meier curves (Guyot algorithm).

Quality assessment / Risk of bias analysis Quality in Prognosis Studies (QUIPS) tool across 6 domains, assessed independently by 2 reviewers. Ancestry (population stratification) is treated as the main confounder and stage, liver function, and treatment as potential mediators; genotyping quality and Hardy-Weinberg equilibrium are assessed under prognostic factor measurement. Overall risk of bias is high if any domain is rated high or at least 3 domains moderate. Certainty of

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evidence is rated with GRADE for prognostic factors.

Strategy of data synthesis Log HRs are pooled with random-effects models (restricted maximum likelihood estimate of τ^2) with Hartung-Knapp (ad hoc) 95% CIs; analyses with 2 studies use a fixed-effect model. Heterogeneity is described with I^2 and τ^2, with 95% prediction intervals for overall analyses of at least 3 studies. Single-study estimates are described narratively. Analyses are performed in R with the metafor package.

Subgroup analysis PNPLA3 association by etiology (metabolic or alcohol-related vs viral or other HCC), including pooling of within-study ratios of HRs; post hoc random-effects meta-regression by HR source (reported vs derived or reconstructed).

Sensitivity analysis Exclusion of reconstructed HRs; restriction to reported, adjusted, or unadjusted HRs; exclusion of studies at high risk of bias in the statistical analysis and reporting domain; exclusion of studies with possible cohort overlap and of the study with the largest deviation from Hardy-Weinberg equilibrium; alternative estimates; inflation of the standard errors of reconstructed HRs by 50%; Wald-type CIs; and leave-one-out analyses.

Language restriction No language restriction.

Country(ies) involved Brazil and United States.

Other relevant information This protocol is registered retrospectively. A protocol focused on PNPLA3 rs738409, with TM6SF2 and HSD17B13 as exploratory co-exposures, was developed before formal screening but was not registered. The review has been completed and has not yet been published. Deviations from that protocol: the scope was extended to MBOAT7 and GCKR, and TM6SF2 and HSD17B13 were analyzed formally; the updated search used PubMed and Europe PMC with citation searching; Hartung-Knapp CIs replaced standard random-effects CIs; study authors were not contacted for missing data; and the analyses of HR source, HSD17B13 homozygosity, stage at diagnosis, and liver function at diagnosis were post hoc.

Keywords hepatocellular carcinoma; PNPLA3; TM6SF2; HSD17B13; MBOAT7; GCKR; prognosis; survival; metabolic dysfunction-associated steatotic liver disease; meta-analysis.

Dissemination plans Publication in a peer-reviewed journal and presentation at scientific meetings.

Contributions of each author

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