Introduction Variants in patatin-like phospholipase domain-containing 3 (PNPLA3; rs738409), transmembrane 6 superfamily member 2 (TM6SF2; rs58542926) and membrane bound O-acyltransferase domain containing 7 (MBOAT7; rs641738) are risk factors for the development of alcohol-related cirrhosis. PNPLA3 rs738409 is also an established risk factor for the development of hepatocellular carcinoma (HCC) within this population. The aim of this study was to explore possible risk associations of TM6SF2 rs58542926 and MBOAT7 rs641738 and the development of HCC.

Methods Risk variants in PNPLA3, TM6SF2 and MBOAT7 were genotyped in 751 cases with alcohol-related cirrhosis and HCC and in 1165 controls with alcohol-related cirrhosis without HCC. Association with the risk of developing HCC was analysed using multivariate logistic regression.

Results The development of HCC was independently associated with PNPLA3 rs738409 (OR 1.84 [95% CI 1.55–2.18], p=1.85×10^{-12}) and TM6SF2 rs58542926 (OR 1.66 [1.30–2.13], p=5.13×10^{-05}) using an additive model and after controlling for sex, age, body mass index and type 2 diabetes mellitus; the risk associated with carriage of MBOAT7 rs641738 (OR 1.04 [0.88–1.24], p=0.61) was not significant. The population-attributable fractions were 43.5% for PNPLA3 rs738409, 11.5% for TM6SF2 rs58542926, and 49.9% for carriage of both variants combined.

Conclusions Carriage of TM6SF2 rs58542926 is an additional risk factor for the development of HCC in people with alcohol-related cirrhosis. Carriage of both PNPLA3 rs738409 and TM6SF2 rs58542926 accounts for half of the attributable risk for HCC in this population. Genotyping will allow for more precise HCC risk stratification of patients with alcohol-related cirrhosis, and genotype-guided screening algorithms would optimise patient care.