Insulin Resistance and Genetic Risk Predict Liver-Related Outcomes and Death in Nonalcoholic Fatty Liver Disease

TO THE EDITOR:

With a globally heightened awareness of nonalcoholic fatty liver disease (NAFLD), the early identification of patients at risk for cirrhosis becomes an imperative. Current recommended risk-stratification strategy aims to capture liver fibrosis, a preclinical state of cirrhosis that predicts liver-related outcomes.[1] An alternative strategy is to use clinically measurable risk factors that drive NAFLD progression. We recently showed that a pathophysiological risk score (PRS) combining insulin resistance (IR) and genetic risk score can predict NAFLD histology.[2]

To validate this model built on cross-sectional observations, we evaluated whether the PRS predicts incident liver-related outcomes in the FINRISK 1992-2012 and Health 2000 surveys, Finnish cross-sectional population surveys.[3] Subjects were linked with the National Registries for Hospitalizations, Death, and Cancer, to determine new diagnoses of cirrhosis, liver cancer, or liver-related mortalities.[4] Individuals with NAFLD at baseline, defined as a Fatty Liver Index score of 60 or higher,[5] were included. Individuals with at-risk drinking (>20 g of ethanol/day in women, >30 g/day in men), viral hepatitis, or other preexisting liver diseases were excluded. The PRS at baseline was calculated using age, homeostasis model assessment of IR (HOMA-IR), and the pres*ence of risk alleles in PNPLA3* (patatin-like phospholipase domain containing 3) or *TM6SF2* (transmembrane 6 superfamily 2), using the equation from our previous study: PRS = 0.072 * age (years) + 0.262 * PNPLA (n alleles) + 1.087 * TM6SF2 (n alleles) + 0.037 * (HOMA-IR/0.1006) – 0.1174.[2] Subjects were divided into PRS tertiles, and Kaplan-Meier analysis was performed with liver-related events as the outcome.

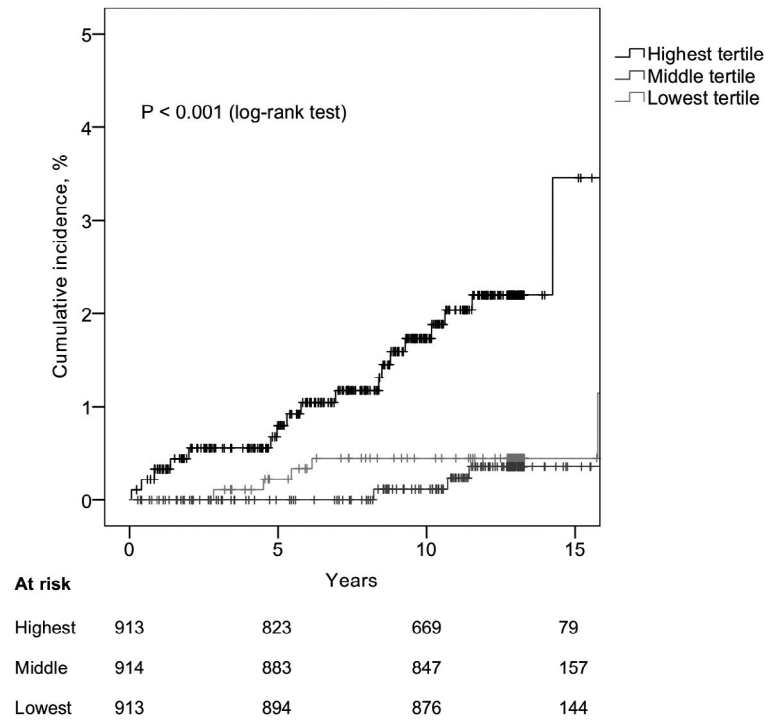

FIG. 1. Cumulative incidence of advanced liver disease by Kaplan-Meier analysis stratified by tertiles of the pathophysiologic risk score. With a median follow-up of 13 years, most (68%) of the liver-related events occurred in the highest-risk tertile.

Among 9,796 individuals with sufficient data to calculate the PRS, 2,740 (28%) had NAFLD and were included in the study (mean age of 57 years [SD = 12], 54% male, mean HOMA-IR = 3.6 [SD 6.8], 38% *PNPLA3* I148M carriers, and 12% *TM6SF2* E167K carriers). Over a median follow-up of 13 years (interquartile range 8-18), 28 incident liver-related events occurred in the NAFLD cohort, among whom 19 (68%) happened in the highest-risk tertile of PRS (hazard ratio 3.95, 95% confidence interval 1.57-9.91, compared with the lowest tertile) (Fig. 1). For comparison, there were 105 incident liver–related events in the general cohort of 9,796 individuals. The PRS showed moderate discrimination for incident liver events (C-statistic = 0.704). A model consisting of only age and HOMA-IR performed similarly (C-statistic = 0.699); however, the improved discrimination with the addition of genetics was significant ($P < 0.001$ by likelihood-ratio test). Note that the discriminant power of genetics is likely underestimated here, because the potential selection bias of the Fatty Liver Index favors NAFLD with conventional phenotypes of high body mass index and fasting triglycerides over patients driven primarily by genetics.

In keeping with our growing knowledge, the observation here demonstrates that liver-related outcomes in NAFLD are largely predictable by genetics and IR in the general population. PRS, a non-liver-centric model based on the pathophysiology of NAFLD, is a viable strategy to risk-stratify NAFLD in the community especially, in places where access to specialty care is limited, and furthermore enables us to tackle the risk factors before development of advanced fibrosis in NAFLD.

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