Editorial Commentary

Heterogeneity in the risk of incident liver cirrhosis driven by *PNPLA3* genotype and diabetes among different populations

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Advanced fibrosis determines the prognosis of nonalcoholic fatty liver disease (NAFLD); therefore, accurate risk-prediction for advanced fibrosis is fundamental in the management of NAFLD (1). Targeted screening for advanced fibrosis in high-risk populations, such as those with type 2 diabetes, obesity with metabolic complications, a family history of cirrhosis, or significant alcohol use is recommended for implementing early intervention to prevent future adverse hepatic outcomes of NAFLD (2,3). Non-invasive tests including fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM) are recommended to identify individuals at a higher risk of liver-related events (1,2). In addition to clinical classifications, such as FIB-4; genetic information provides further stratification for liver-related outcomes (4).

Recently, Chen *et al.* reported that the *PNPLA3*-rs738409 genotypes and diabetes status identified patients at a higher risk of cirrhosis among those already at an indeterminate risk of NAFLD (FIB-4: 1.3–2.67) in two independent cohorts involving the Michigan Genomics Initiative (MGI) and United Kingdom Biobank (UKBB). NAFLD patients with FIB-4: 1.3–2.67, in the presence of *PNPLA3*-rs738409 GG genotype and diabetes had a cirrhosis incidence-risk comparable to those with FIB-4 >2.67 (5).

Since the participants from MGI and UKBB were mainly Caucasians; we investigated whether the occurrence of diabetes and *PNPLA3*-rs738409 GG genotype identified at-risk population with NAFLD carrying an intermediate risk using an Asian biopsy-proven NAFLD cohort (6). Based on serial assessments of LSM by transient elastography, at least 1 year apart (n=267), fibrosis progression was defined as a composite of (I) LSM ≥9.6 kPa during the follow-up period for patients with F0–2 at baseline (7), and (II) ΔLSM ≥+20% compared to the baseline level during the follow-up period for patients with F3–4 at baseline (8). According to baseline FIB-4 values (<1.3, 1.3–2.67, >2.67), diabetes status, and *PNPLA3* genotype, the risk of fibrosis progression was assessed using the Cox proportional hazards model. Compared to those with FIB-4 <1.3 at baseline and CC + CG genotype, individuals with FIB-4 1.3–2.67, diabetes, and GG genotype showed 8.52 times higher risk of fibrosis progression [95% confidence interval (CI): 2.13–34.08; *Figure 1*], which was not statistically different from that of individuals with FIB-4 >2.67 (P=0.550), corresponding to the result by Chen *et al.*

Chen *et al.* suggested that NAFLD with FIB-4: 1.3–2.67, diabetes, and GG genotype could be categorized as the high-risk group (5). However, the difference in the

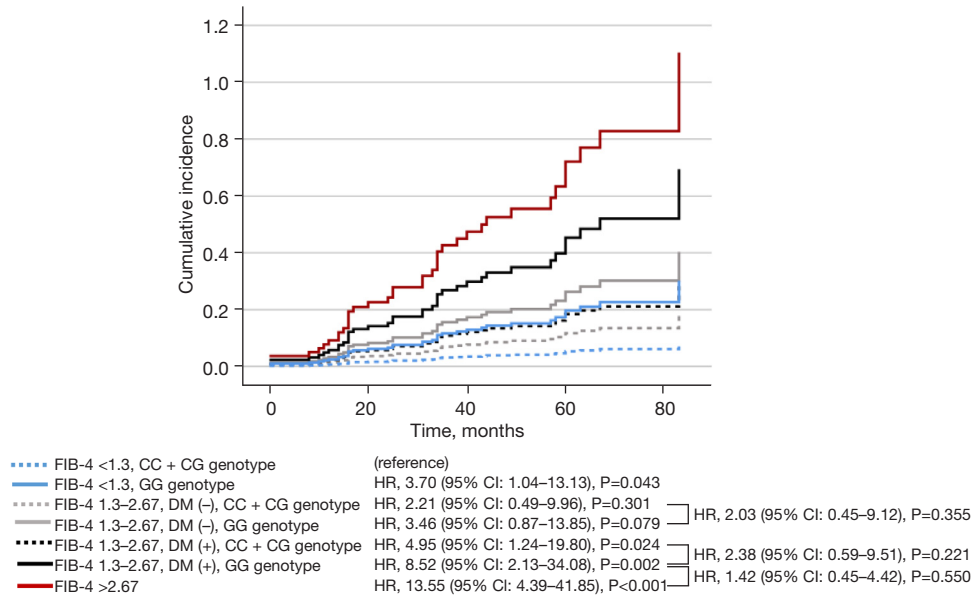

Figure 1 The risk of fibrosis progression according to *PNPLA3* rs738409 genotype and diabetes at baseline in FIB-4 <1.3, 1.3–2.67, and >2.67 at baseline. The cumulative incidence of fibrosis progression in patients with NAFLD, which was defined as LSM ≥9.6 kPa for patients with F0–2 at baseline and ΔLSM ≥+20% compared to the baseline level for patients with F3–4 at baseline during the follow-up period. FIB-4, fibrosis-4 index; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; LSM, liver stiffness measurement.

effect of *PNPLA3* genotype on the risk of cirrhosis and the difference in the absolute incidence-rate of cirrhosis between individuals from MGI and UKBB, should be carefully interpreted to apply the risk-stratifying strategy in a clinical setting.

MGI and UKBB are prospective cohorts based on the tertiary care center and community, respectively (5). Due to this fundamental difference in participants from MGI and UKBB, there were marked differences in the prevalence of cardiometabolic risk factors between the cohorts (5). The prevalence of diabetes and obesity was higher in MGI compared to that of UKBB (diabetes: 35.5% *vs.* 9.7%; obesity: 57.0% *vs.* 46.2%). Moreover, the prevalence of class III obesity and coronary heart disease in MGI reached 14.9% and 20.2%, respectively, which were agreeably higher than 4.0% and 8.8% in UKBB (5). Despite the lack of data on the sensitivity of ICD-9/10 code-based definition of cirrhosis in each cohort, the difference in cirrhosis-incidence between MGI and UKBB during the follow-up period may correspond to the difference in the cardiometabolic risk found in these cohorts at baseline. The incidence of cirrhosis was 4.0 per 1,000 person-years (PY) (median follow-up, 71.6 months) and 0.6 per 1,000 PY (median follow-up, 106.3 months) in MGI and UKBB, respectively (5). In MGI, even those with FIB-4 <1.3, no diabetes, and the presence of GG genotype showed a higher incidence-rate of cirrhosis (7.68 per 1,000 PY) than patients with NAFLD from UKBB with FIB-4: 1.3–2.67, diabetes, and GG genotype (3.72 per 1,000 PY). As suggested by Chen *et al.*, NAFLD with FIB-4: 1.3–2.67, diabetes, and GG genotype may be categorized as the high-risk group; however, individuals satisfying these criteria in UKBB showed a lower incidence of cirrhosis than those with NAFLD and FIB-4 <1.3 from the hospital-based cohort. In MGI, the *PNPLA3* genotype can identify those at a high risk of incident cirrhosis in individuals with FIB-4 <1.3 and no diabetes (CC + CG, 1.93 per 1,000 PY; GG, 7.68 per 1,000 PY). Moreover, the effect of *PNPLA3* genotype on cirrhosis-incidence was more pronounced in individuals without diabetes as opposed to those with diabetes [incidence rate ratio, 3.98 (95% CI: 3.00–5.27) *vs.* 0.80 (95% CI: 0.10–6.35)].

The heterogeneity in the effect of *PNPLA3* genotype on NAFLD progression should be also considered in the development of risk-stratifying model incorporating genotypes. Using PubMed and Embase, we searched for studies investigating the association between the *PNPLA3* genotype and NAFLD severity. Inclusion criteria were studies with (I) liver biopsy or magnetic resonance imaging to define NAFLD or nonalcoholic steatohepatitis (NASH),

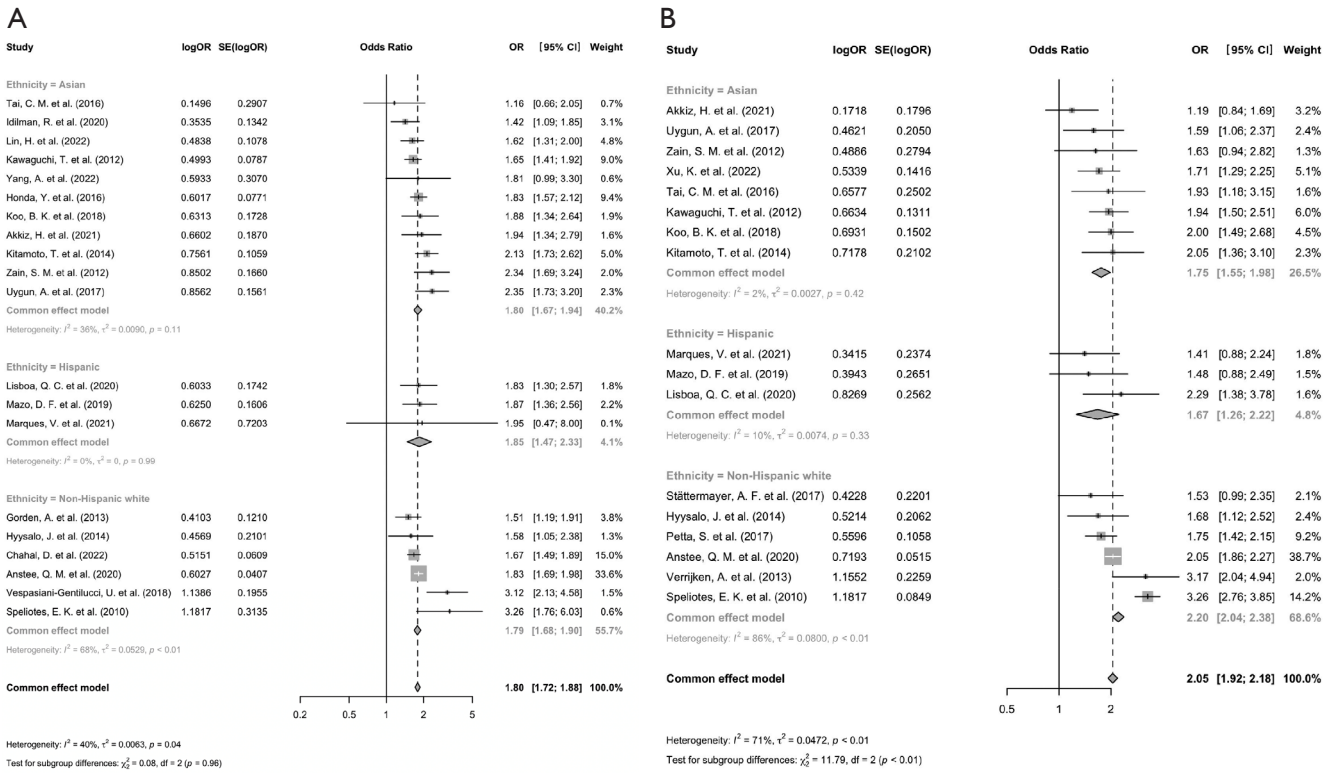

Figure 2 The ethnic difference in the risk of NAFLD according to *PNPLA3* rs738409 genotype. Meta-analysis for the ethnic difference in the risk of NAFLD (A) and NASH among NAFLD subjects (B), according to *PNPLA3* rs738409 genotype. OR, odds ratio; SE, standard error; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

(II) *PNPLA3* rs738409 genotype, and (III) information on the ethnicity of study subjects. Exclusion criteria were studies with (I) study subjects <100, (II) absence of ethnicity data, (III) no genotype-matched outcomes, or (IV) abstracts or posters only. Among the 1,044 articles identified through database searching, 20 studies were included in the analysis. Overall, the risk of NAFLD increased 1.80 times (95% CI: 1.72–1.88) per 1G allele (*Figure 2A*). There was no ethnic difference in the effect of *PNPLA3* genotype and NAFLD (P=0.960). Instead, significant heterogeneity among the studies in each ethnic group as well as in the entire studies was found (P=0.018 and 0.030, respectively). The association between *PNPLA3* genotype and NASH in NAFLD population based on ethnicity was also analyzed, and statistically significant heterogeneity was found (P<0.001; *Figure 2B*).

It must be acknowledged that diabetes and *PNPLA3* genotype are important factors for determination of liver cirrhosis in NAFLD. However, the absolute risk associated with the presence of risk factors in NAFLD patients may vary across the study populations. The expert guidelines recommend that the approach for evaluating the risk of advanced NAFLD should be based on the prevalence of advanced disease in each population (2). As compared to hepatology practices, the objective of risk assessment in a primary healthcare setting is to identify patients who are unlikely to have advanced fibrosis as the prevalence of advanced NAFLD may be relatively low (2,3). To establish the risk-stratifying strategy, the prevalence of advanced liver disease and co-morbidities associated with NAFLD severity in the target population should be considered (9). When predicting the risk, particularly through the use of risk genotypes, it is essential to consider the heterogeneity in the effects of genotypes within each population.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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