Commentary

Nonalcoholic fatty liver disease in early life and all-cause and cause-specific mortality

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Nonalcoholic fatty liver disease (NAFLD) is the most prevalent cause of chronic liver disease worldwide. In most individuals with NAFLD, liver histology is typically characterized by nonalcoholic fatty liver (NAFL), while up to 20% are noted to have nonalcoholic steatohepatitis (NASH) with or without fibrosis. The stage of NAFLD-related hepatic fibrosis and not the presence of NASH is associated with the risk of all-cause and cause-specific mortality (1,2). During the recent decade, NAFLD-associated advanced fibrosis increased in prevalence in the United States (US) from 3% among individuals with NAFLD in 2005–2008 to 6% in 2013–2016, estimated to be four million US adults (3). Notably, mortality for NAFLD-associated cirrhosis increased significantly between 2007 and 2016, with an annual increase of 15.4% (4). Although earlier studies showed that NAFLD was associated with higher mortality than the general population of the same age and sex (5), it is not clear whether more severe NAFLD is associated with the underlying metabolic complications responsible for the increased risk of all-cause and cause-specific mortalities. A US population-based study with 15 years of follow-up reported that NAFLD by itself did not increase the risk of mortality, whereas NAFLD with advanced fibrosis was associated with an increase in all-cause and cardiovascular mortality (2). After adjustment for multiple clinical and metabolic confounders beyond age and sex, NAFLD was no longer predictive of all-cause mortalities (2). A recent meta-analysis validated that the risk of all-cause and liver-related mortality increases with an increase in fibrosis stage in individuals with NAFLD (1). In addition, better phenotyping of NAFLD may be warranted to investigate the relationship of NAFLD with mortality. A US population-based study showed that individuals with metabolic (dysfunction)-associated fatty liver disease had a higher risk of all-cause mortality even after adjusting for metabolic risk factors, while NAFLD *per se* did not increase the risk (5). Another study reported that low thyroid function in individuals with NAFLD predicts a higher risk for all-cause and cardiovascular mortality (6). Therefore, it is essential to identify and phenotype high-risk subpopulations at increased risk of all-cause mortality among individuals with NAFLD.

Given the high prevalence of obesity and type 2 diabetes in the adult and pediatric population, it is not surprising to observe the rising rates of NAFLD in both children and young adults (7). A study based on the 2009–2019 Global Burden of Disease (GBD) determined an increasing trend in the prevalence of NAFLD among adolescents and young adults (age: 15–29 years) in the world (8). Although the all-cause mortality from chronic liver disease decreased worldwide among adolescents and young adults during recent decades, all-cause mortality for NAFLD increased with an annual rate of 2.3% in the young population from 2015 to 2019 (8). Unfortunately, current data on the natural history of NAFLD early in life remain scant and undefined (9). A recent nationwide study from Sweden sheds light on the natural history of NAFLD in children and young adults (10). This nationwide, matched cohort study included all Swedish children and young adults (≤25 years) with biopsy-confirmed NAFLD from 1966

to 2017 (n=718) (10). NAFLD, which was categorized as NAFL or NASH, was defined histologically from results of liver biopsies through topography and morphology code (10). Over 20 years, the absolute risk of all-cause mortality was 7.7% among individuals with NAFLD and 1.1% among controls matched to age, sex, calendar year, and county, which translated into one additional death per every 15 individuals with NAFLD (10). After multivariable adjustment, individuals with NAFLD had 5.9-fold higher mortality than matched controls [hazard ratio (HR): 5.88; 95% confidence interval (CI): 3.77–9.17]. The 20-year absolute mortality risk was 5.7% higher with NAFL (95% CI: 2.8–8.6) and 8.4% higher with NASH (95% CI: 3.2–13.6) than the control group. Regarding cause-specific mortality, NAFLD was associated with a higher risk of mortality from liver disease (HR: 16.46; 95% CI: 2.75–98.43), cancer (HR: 15.60; 95% CI: 4.97–48.93), and cardiometabolic disease (HR: 4.32; 95% CI: 1.73–10.79), respectively. These findings persisted when individuals with NAFLD were compared to their full siblings, rendering it unlikely that inherited or early-life risk factors fully explain the substantial burden of excess mortality associated with NAFLD (10). Although NASH with fibrosis was associated with increased mortality, the magnitude of risk did not differ significantly from NASH without fibrosis (10). While this nationwide biopsy-proven study demonstrated that NAFLD in early life was associated with a high risk of all-cause and cause-specific mortality, we must interpret and extrapolate these findings with caution. Over 50 years, 718 individuals with biopsy-proven NAFLD were enrolled in this study, leading to a high potential for selection bias. Individuals with NAFLD referred to a tertiary center may have a more advanced disease than those diagnosed and managed in the community. It is plausible that individuals with more severe liver disease underwent a liver biopsy based on a constellation of features and clinical suspicion leading to a selection bias. The attempt to match with the general population resulted in a notable discrepancy of cardiovascular disease, diabetes, and other metabolic comorbidities between the two groups, although the authors attempted to adjust for these metabolic comorbidities. The inter-and intra-rater agreement on lobular inflammation and hepatocyte ballooning was noted as low or modest. The authors defined NAFLD using text results of liver biopsies through topography and morphology code from 28 Swedish pathology departments over 50 years. Therefore, this method to describe and assess the histological features and severity of NAFLD in a liver biopsy database may have resulted in misclassification.

With these caveats in mind, this nationwide, population-based cohort of children and young adults provided valuable evidence to our understanding of NAFLD in the special sub-population. NAFLD was associated with an increased risk of all-cause mortality, and most of the excess deaths were derived from malignancy, liver disease, or cardiometabolic disease. The magnitude of higher risk of all-cause mortality was amplified in patients with NASH. A multidisciplinary effort is needed for prevention, risk stratification, and surveillance strategies in order to improve long-term outcomes for this rapidly increasing cohort of children and young adults.

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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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