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Nonalcoholic Fatty Liver Disease Activity Score and Mortality: Imperfect But Not Insignificant

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To the Editor

Recently, Ekstedt et al.[1] reported the results of a longitudinal study evaluating mortality in nonalcoholic fatty liver disease (NAFLD). Evaluation of outcomes in NAFLD is often limited by a long interval between diagnosis and clinical events; however, with mean follow-up of 26 years, this study stands out as one of the largest long-term evaluations of health consequences among persons with NAFLD. The investigators concluded that persons with NAFLD have increased overall and disease-specific mortality compared to sex- and age-matched controls, and that the NAFLD activity score (NAS) was not a predictor of increased mortality. Instead, the study concludes that advanced fibrosis was the most useful marker of mortality in patients with NAFLD.

We agree with the investigators that the NAS needs to be revisited as an endpoint for clinical trials. In particular, there has long been recognition of hepatic fat loss in advanced fibrosis,[2] suggesting that even as a patient's disease progresses, the steatosis score and thereby the NAS may decrease. However, their conclusion that overall mortality was not increased in patients with NAS 5-8 and fibrosis stage 0-2 is a misinterpretation of their results. The Cox regression analysis yielded a hazard ratio of 1.41 (95% confidence interval [CI]: 0.97-2.06; $P = 0.07$) for the association between NAS 5-8 and fibrosis stage 0-2 and mortality. Despite having interpreted a smaller hazard ratio of 1.29 as “increased mortality” for all patients with NAFLD, they interpreted the hazard ratio of 1.41 as “mortality was not increased” for NAS 5-8 and fibrosis 0-2, apparently ignoring the estimated hazard ratio and relying only on the fact that the P value was (slightly) above 0.05. $P > 0.05$ is not reliable evidence for a negative conclusion, and the estimate is the possible true value that is most supported by the data. Failing to reject the null hypothesis does not prove that the null hypothesis is true—it means that the results could be owing to chance, not that they must be owing to chance. In fact, the estimated hazard ratio and its 95% CI provide evidence that a NAS of 5-8 without advanced fibrosis is associated with increased mortality, because the estimate and almost all of the CI are above 1. Indeed, a doubled risk of death is as compatible with their data as no increase in risk. A hazard ratio near 1.0 with a narrow CI around it would provide strong evidence against a substantial increase in mortality, but this is not what this study found. The increased hazard ratio for hepatocellular carcinoma HCC, 15.7 (95% CI: 4.1-59.9; $P <$

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0.001), among patients with NAS 5-8 and fibrosis 0-2 further calls into question any conclusion that patients with a high NAS without fibrosis have a benign course.

The conclusion that advanced fibrosis is associated with increased mortality compared to a referent population remains an important finding and the increased risk of mortality resulting from cardiovascular and liver-specific causes highlight the importance of identifying at-risk persons with the goal of targeted surveillance and interventions. Certainly, consideration should be given to including fibrosis stage and de-emphasizing steatosis in future scoring systems for NAFLD, while continuing to search for non-invasive assessments of disease severity to mitigate the sampling variability associated with liver biopsy.[3] However, though the NAS is an imperfect prognostic tool, the study from Ekstedt et al. should not lead us to conclude that patients with an increased NAS without advanced fibrosis will have a benign disease course. Pending more definitive studies, it seems prudent to continue monitoring of this subgroup of NAFLD patients for long-term complications.

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