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Letters

Nonalcoholic Fatty Liver Disease and Incident Cardiac Events

The Multi-Ethnic Study of Atherosclerosis

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in the general population, with an estimated prevalence of 20% to 30% (1). The risk factors for atherosclerosis and fatty liver have a significant overlap, and recent studies show NAFLD to be a strong predictor of the incidence of cardiovascular disease (CVD) (2). However, it is not clear yet whether NAFLD is associated with CVD as a result of shared risk factors or whether it contributes to atherosclerotic CVD independently.

The current study evaluated whether NAFLD is associated with incident nonfatal coronary heart disease (CHD) and all-cause mortality events independent of traditional risk factors, C-reactive protein (CRP), and coronary artery calcium (CAC) and whether the predictive value of NAFLD provides any useful additive value to the traditional risk factors in risk stratification.

The MESA study (Multi-Ethnic Study of Atherosclerosis) included 6,814 participants, 45 to 84 years of age, who were free of clinical CVD at baseline. All participants gave informed consent, and the institutional review board at each site in accordance with the Health Insurance Portability and Accountability Act requirements approved the study protocol. Each participant underwent 2 consecutive nonenhanced cardiac computed tomography scans during a single session. Two independent readers for liver fat measurement evaluated the scans, the details of which were published previously (3). A liver-to-spleen ratio <1.0 was taken as the cutoff point for the diagnosis of the presence of liver fat.

For the purposes of this study, we defined incident nonfatal CHD as the first occurrence of myocardial infarction, resuscitated cardiac arrest, definite or probable angina followed by coronary revascularization, and definite angina not followed by coronary revascularization. All-cause mortality was used for Kaplan-Meier analysis. These participants were followed over a median duration of 7.6 years.

Initially there were 6,814 MESA study participants who had computed tomography scans at the baseline. We were able to measure liver-to-spleen ratio in 4,376 participants. Among the remaining 4,376 participants, 257 study participants were excluded from the analysis: 178 with heavy alcohol intake (defined as >14 drinks per week for men and >7 drinks per week for women), 68 taking oral steroids, 5 with self-reported cirrhosis, 2 with oral antiarrhythmic drug use, and 4 with missing follow-up information. The final population comprised 4,119 participants. The body mass index and the clinical characteristics of the participant population who were excluded were comparable to those included in the study except age, race, low-density lipoprotein (LDL), and hypertension. Participants with NAFLD ($n = 728$) were slightly younger (61 ± 9 years vs. 63 ± 10 years, $p < 0.0001$) and had a higher prevalence of hypertension (53% vs. 46%, $p < 0.0001$) and diabetes mellitus (22% vs. 11%, $p < 0.0001$) and higher LDL (117 ± 31 mg/dl vs. 115 ± 31 mg/dl, $p = 0.04$), high-density lipoprotein (HDL) (52 ± 15 mg/dl vs. 45 ± 12 mg/dl, $p < 0.0001$), and body mass index (28 ± 5.2 kg/m^2 vs. 31 ± 5.4 kg/m^2, $p < 0.0001$) levels compared with those without liver fat ($n = 3,391$).

During a median follow-up duration of 7.6 years, a total of 209 participants (5.1%) were noted to have a composite of nonfatal CHD events (myocardial infarctions, $n = 97$; angina, $n = 148$; revascularization, $n = 155$). There were 253 deaths reported (all-cause mortality), 40 participants with NAFLD and 213 without NAFLD. Kaplan-Meier survival curves (**Figure 1A**) showed significantly decreased survival among those with NAFLD compared with those without NAFLD. On Cox regression analyses, NAFLD was associated with incident nonfatal CHD and all-cause mortality events after adjusting for age, sex, ethnicity, and MESA study sites (hazard ratio [HR]: 1.74, 95% confidence interval [CI]: 1.25 to 2.41, $p = 0.01$). For Cox regression analyses, a composite endpoint inclusive of nonfatal CHD and all-cause mortality events was used. NAFLD remained significantly associated with incident nonfatal CHD and all-cause mortality events (HR: 1.43, 95% CI: 1.00 to 2.03, $p = 0.04$) after further adjustment for traditional risk factors (diabetes, hypertension, body mass index,

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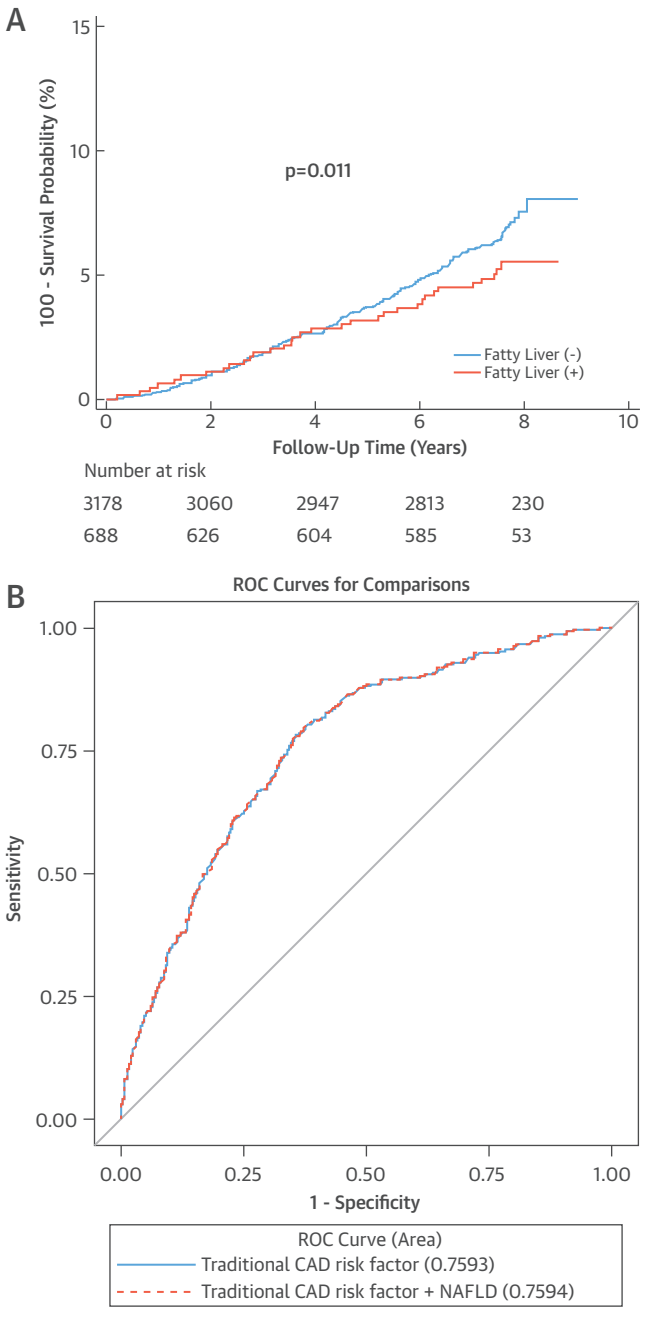
FIGURE 1 All-Cause Mortality: Kaplan-Meier and ROC Analysis



(A) Results of the Kaplan-Meier cumulative curve analysis for all-cause mortality. **(B)** Results of the receiver-operating characteristic (ROC) curve analysis for nonfatal coronary heart disease and all-cause mortality events. Risk factors include age, sex, diabetes mellitus, hypertension, dyslipidemia, and smoking. CAD = coronary artery disease; NAFLD = nonalcoholic fatty liver disease.

LDL, HDL, triglycerides, smoking, family history of CHD, cholesterol-lowering medications), and traditional risk factors plus CRP (HR: 1.42, 95% CI: 1.00 to 2.02, p = 0.05) and, traditional risk factors plus CRP and CAC (log CAC+1) simultaneously (HR: 1.42, 95% CI: 1.00 to 2.03, p = 0.05).

Figure 1B shows the results of receiver-operating characteristic curve analysis comparing the area under curve for cardiovascular risk factors and NAFLD added to cardiovascular risk factors. There was no significant difference in the area under the curve for cardiovascular risk factors alone and NAFLD with cardiovascular risk factors for a composite of nonfatal CHD and all-cause mortality events (p > 0.05).

In this analysis, we observed NAFLD to be associated with incident nonfatal CHD and all-cause mortality events independent of traditional cardiovascular risk factors, CRP, and coronary atherosclerosis burden. However, in contrast to previous evidence, NAFLD did not provide any improved discrimination value for the traditional risk factors in risk stratification in our analysis. NAFLD may independently predict future CHD events and may act in concert with other cardiovascular risk factors in the pathogenesis of atherosclerosis.

*Irfan Zeb, MD
Dong Li, MD
Matthew J. Budoff, MD
Ronit Katz, PhD
Donald Lloyd-Jones, MD
Arthur Agatston, MD
Roger S. Blumenthal, MD
Michael J. Blaha, MD
Ron Blankstein, MD
Jeffrey Carr, MD
Khurram Nasir, MD, MPH

*Department of Cardiology
Mount Sinai St. Luke's Hospital
1111 Amsterdam Avenue
New York, New York 10025
E-mail: izeb82@gmail.com

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