

Age, impaired fasting glucose, and cirrhosis predicted mortality at mean 7.6 years for nonalcoholic fatty liver disease

Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005;129:113-21.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Gastroenterology ★★★★★☆☆

QUESTION

What is the natural history of nonalcoholic fatty liver disease (NAFLD) in community-based patients?

METHODS

Design: Inception cohort followed for mean 7.6 years (range 0.1 to 23.5 y).

Setting: Olmsted County in southeastern Minnesota, United States.

Patients: 435 patients (mean age 49 y, 51% women, 92% white) diagnosed with NAFLD, fatty liver, hepatic steatosis, steatohepatitis, or cryptogenic cirrhosis (confirmed by ultrasonography, computed tomography, or magnetic resonance imaging) between 1 January 1980 and 1 January 2000. Exclusion criteria included other liver disease, risk for viral hepatitis, secondary causes of fatty liver (medications, HIV, or gastrointestinal bypass surgery), and average weekly ethanol consumption ≥ 140 g.

Prognostic factors: Age, sex, ethnicity, body mass index, average weekly alcohol intake, history of diabetes (fasting glucose ≥ 126 mg/dL [6.93 mmol/L] or receiving treatment), impaired fasting glucose (IFG) (fasting glucose ≥ 110 mg/dL [6.05 mmol/L]),

hypertriglyceridemia (fasting triglyceride ≥ 150 mg/dL [8.25 mmol/L]), low fasting high-density lipoprotein cholesterol (< 40 mg/dL [2.2 mmol/L] for men and < 50 mg/dL [2.75 mmol/L] for women), hypertension ($\geq 130/\geq 85$ mm Hg or receiving treatment), ischemic heart disease (defined as previous myocardial infarction or angina pectoris), cerebrovascular disease (defined as previous cerebrovascular accident or transient ischemic attack), and cirrhosis at baseline.

Outcomes: All-cause mortality and liver-related mortality.

MAIN RESULTS

Mortality in patients with NAFLD was higher than that in the general population (standardized mortality ratio 1.34, 95% CI 1.003 to 1.76, $P = 0.03$). Age, IFG or diabetes, and

cirrhosis at baseline were associated with increased mortality (Table). Liver-related death occurred in 7 patients (1.7%) and was the third leading cause of death after cancer and ischemic heart disease, compared with the thirteenth cause of death in the general population. 13 patients (3.1%) developed liver-related complications at mean 7.6 years.

CONCLUSIONS

In patients with nonalcoholic fatty liver disease, mortality was higher than that of the general population. Age, impaired fasting glucose, and cirrhosis at baseline predicted higher mortality.

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Baseline predictors for mortality in nonalcoholic fatty liver disease at mean 7.6 years*

Prognostic factors	Hazard ratio (95% CI)	P value
Age (per decade)	2.2 (1.7 to 2.7)	< 0.001
Impaired fasting glucose or diabetes	2.6 (1.3 to 5.2)	0.005
Cirrhosis	3.1 (1.2 to 7.8)	0.02

*Survival analysis excluded 15 patients diagnosed with postmortem nonalcoholic fatty liver disease.

COMMENTARY

The recognition that NAFLD/nonalcoholic steatohepatitis (NASH) can lead to cirrhosis and hepatocellular cancer is important. Sonographic evidence of NAFLD/NASH in population-based cohorts is found in almost 20% of normal-weight persons and 80% of overweight persons (1).

The study by Adams and colleagues is the first population-based cohort study to assess the effect of NAFLD/NASH on survival in a large number of patients. They found that mortality was increased by 34% in NAFLD and that age, IFG, and cirrhosis were predictors of mortality. 13 patients (3.1%) developed liver-related complications. The authors rightfully pointed out that their data were more representative of the general population than previous reports and that the mortality rate from liver disease was lower than in cohorts from hepatology centers. They postulated that 1 in 30 patients might develop cirrhosis.

What are the implications of this study for daily practice? First, the cohort consisted of 420 patients, although > 42 000 patients may be affected by NAFLD/NASH, based on the postulated prevalence of 34% in the population of 124 000 persons in Olmsted county. If taken at face value, this would decrease cirrhogenesis to 1 in 3000 rather than the quoted figure of 1 in 30. The predictors of death are also not very helpful. It seems intuitive that patients with established cirrhosis are

more likely to die, and that age would be a significant prognostic factor in multivariate analysis. The identification of IFG as a predictor supports other published reports that insulin resistance is one of the first events in NAFLD/NASH (2).

A question that remains unanswered for the internist and general practitioner is what to do with the patient with marker-negative liver disease who is suspected of having NAFLD/NASH. The study by Adams and colleagues would suggest that we could remain conservative with the biopsy needle since hepatic mortality is low, and excess mortality is probably caused by complications of diabetes.

A bigger question that this study does not answer to my satisfaction is how we can differentiate between NAFLD and NASH, assuming that only the latter progresses to cirrhosis and liver cancer. A prospective, biopsy-based study is clearly needed.

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References

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