Patients With Lean Nonalcoholic Fatty Liver Disease Are Metabolically Abnormal and Have a Higher Risk for Mortality

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IN BRIEF Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognized and common cause of chronic liver disease worldwide. Although most patients with NAFLD are obese, a smaller group of NAFLD patients are lean. This study explored the long-term outcomes of lean patients with NAFLD in the United States. Compared to lean individuals without NAFLD, lean people with NAFLD were significantly more likely to be older and male and had higher comorbidities (i.e., diabetes, hyperlipidemia, hypertension, metabolic syndrome, chronic kidney disease, and cardiovascular disease). The presence of NAFLD in lean individuals was independently associated with increased risk of all-cause and cardiovascular mortality.

Nonalcoholic fatty liver disease (NAFLD) is a major cause of liver disease worldwide (1,2). NAFLD is defined as the presence of hepatic steatosis in the absence of secondary causes of fatty liver and chronic infections with hepatitis B and C viruses, excessive alcohol intake, medications, and some hereditary disorders that induce steatosis (3–5). NAFLD can lead not only to adverse clinical outcomes, but also to patient-reported outcomes such as impairment of health-related quality of life (6,7).

Although the prevalence of NAFLD shows variations across different regions of the world, recent data revealed that the global prevalence of NAFLD is ~25% (8). In fact, this prevalence is even higher in some specific populations, such as individuals with type 2 diabetes or patients undergoing bariatric surgery (3,4,7–9). A number of studies have shown that the prevalence of NAFLD has been increasing for the past two to three decades, and this trend is projected to increase in parallel with the global epidemic of obesity (9,10). Although most NAFLD patients are obese or overweight, some individuals with NAFLD are lean (10,11). Some recent data suggest that the prevalence of lean NAFLD is higher in some areas of the world, especially in the rural areas of Asian countries (12). Although long-term outcomes of the typical obese NAFLD cohort has been reported (8–10,13,14), the long-term outcomes of lean NAFLD subjects from the United States are not available. Therefore, the aim of this study was to determine the long-term outcomes of lean patients with NAFLD using U.S. population data from the third National Health and Nutrition Survey (NHANES III database.

Methods

NHANES III is a cross-sectional, population-based sample survey of the civilian noninstitutionalized population of the United States. Surveys were based on a complex, multistage sampling plan. The cross-sectional NHANES III nationally based survey cohort has been described in detail previously (15,16). The survey consists of a household interview and

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a medical/laboratory examination carried out in a mobile examination center. Data collected for each participant in the initial cohort included clinical, laboratory, and follow-up mortality data. Of the 20,050 adult participants from NHANES III, we excluded 458 participants not followed for mortality and 4,622 missing primary laboratory variables such as alanine aminotransferase (ALT), triglycerides, or serum insulin. Of 14,970 participants, we excluded 9,120 due to overweight or obesity (BMI >25 kg/m^2). For the purpose of the study, we excluded 475 participants with other causes of chronic liver disease. The final cohort included 5,375 participants (Figure 1).

Participants' age (20–44, 45–54, 55–64, and >65 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other [which included other Hispanics, Asians, and Native Americans]), sex, whether they were a smoker (which included either current smoking or having 100 or more cigarettes during their lifetime), poverty-income ratio (PIR) (PIR <1.3 as low, PIR 1.3 to <3.5 as middle, and PIR >3.5 as high) (16), and health conditions were obtained as self-reported information from the NHANES in-home interview.

Study Covariates

Lean was defined as individuals with BMI ≤25 kg/m^2. Diabetes was defined as having a fasting glucose measure of >126 mg/dL or self-reported medical history of diabetes (17). Hypertension was defined as having systolic blood pressure of >140 mmHg or diastolic blood pressure of >90 mmHg from an average three measurements or history of high blood pressure (18). High total cholesterol was defined as a serum cholesterol level of >240 mg/dL. Insulin resistance (IR) was defined as having a homeostasis model of assessment (HOMA) score of >3. Iron overload was defined as serum transferrin saturation ≥50%. Excessive alcohol consumption was defined as ≥20 g/day in men and ≥10 g/day in women. Alcoholic liver disease was defined by excessive alcohol use and elevated liver enzymes. Chronic hepatitis C was defined as positive hepatitis C virus RNA, and chronic hepatitis B was defined as positive hepatitis B surface antigen. Cardiovascular disease (CVD) was defined by self-reported medical history of congestive heart failure, heart attack, or stroke. Chronic kidney disease (CKD) was defined by either albuminuria or a glomerular filtration rate ≤60 mL/min/1.73 m^2. Serum creatinine measurements were standardized by the NHANES recommendation (16). Albuminuria was defined as a urinary albumin-to-creatinine ratio ≥30 mg/g. Glomerular filtration rate was estimated by using the 2012 CKD

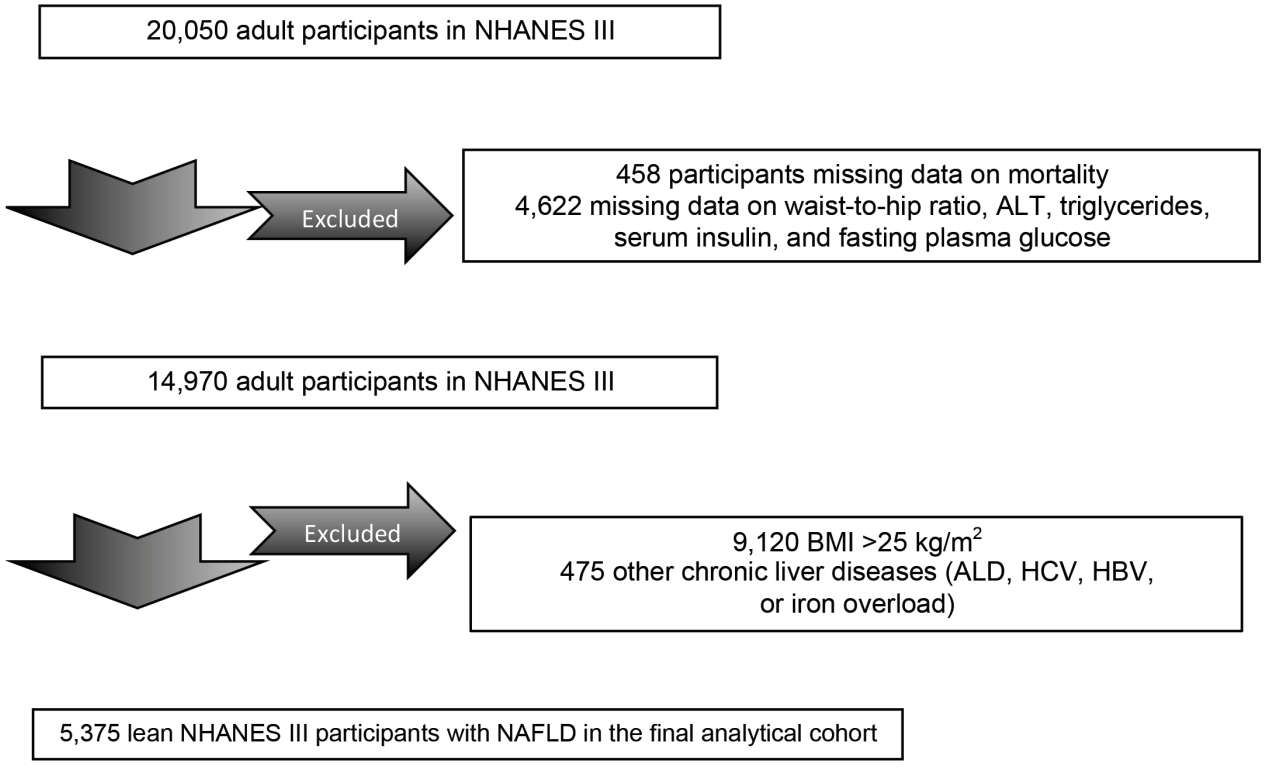

FIGURE 1. Study flow of the analytical cohort selection from NHANES III. ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

Epidemiology Collaboration creatinine equation (19).

Diagnosis of NAFLD

We initially defined NAFLD as presence of fatty liver by hepatic ultrasound examinations in the absence of other causes of chronic liver disease and excessive alcohol consumption. However, for the NHANES, hepatic ultrasound was only performed on those between 20 and 74 years of age, which created a significant bias group. Two other noninvasive tests for diagnosis of fatty liver were considered. These included the fatty liver index and the index of nonalcoholic steatohepatitis (NASH) (20). Since the fatty liver index is based on BMI, it cannot be used for lean patients with NAFLD. On the other hand, the index of NASH (ION) has good predictive performance for establishing the diagnosis of NAFLD (20). ION uses waist-to-hip ratio, ALT, triglycerides, and HOMA. In fact, we initially performed an agreement test between hepatic ultrasound and ION using the NHANES data set and discovered good agreement, with a kappa score of 0.43 between ultrasound and ION. Since ION was available for all patients and had good agreement with ultrasound, we elected to use it as the noninvasive test to determine the presence of NAFLD for the study. In this context, NAFLD was defined as an ION ≥22 in the absence of any other evidence of chronic liver diseases such as alcoholic liver disease, hepatitis B, hepatitis C, iron overload, and other liver diseases as well as excessive alcohol use (20). Non-NAFLD control subjects were defined as those with absence of NAFLD and any other chronic liver disease.

Mortality Data

The NHANES III Linked Mortality File provides follow-up data on vital status from the date of NHANES III survey participation (1988–1994) through the date of death or 31 December 2011. Mortality verification is based on the results from a probabilistic match between NHANES III and the National Death Index (NDI) death certificate records (21). Participants who were not matched with any death records were presumed alive through the follow-up period. Cause of death was attributed by the National Center for Health Statistics (NCHS) based on the *International Classification of Diseases*, 9th or 10th revision. For our study, cardiovascular (CV) mortality was defined as death due to diseases of the heart (codes I00-I90, I11, I13, and I20–I51) (22).

Statistical Analysis

The complex survey design elements (clusters, strata, and examination sample weights) provided by NCHS were used to account for the differential selection probabilities, survey nonresponse and noncoverage, and oversampling of older people, black people, and Mexican Americans. Sampling errors were estimated by the Taylor series linearization (23). Data were articulated as weighted means or percentages with SE. Diverse characteristics were compared by NAFLD status among lean individuals using a *t* statistic for continuous variables and the Rao-Scott χ^2 test for categorical variables. Cox proportional hazards models were used to ascertain the associations of NAFLD with all-cause or CV mortality in lean individuals while adjusting for demographic variables, metabolic components, and comorbidities. The proportional hazards assumption of the Cox models was examined by testing time-dependent covariates (24). All analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, N.C.). Statistical tests were considered significant at P <0.05 (two tailed).

Results

General Characteristics of the Total Cohort

A total of 20,050 NHANES III participants were considered. After inclusion and exclusion criteria, 5,375 subjects were considered the study cohort (Figure 1). Of the study cohort, 581 (10.8%) had NAFLD and 4,794 were considered non-NAFLD control subjects. Compared to lean control subjects, the lean NAFLD group was older, more likely to be Hispanic, had lower income, and had reported poorer health and more comorbidities (Table 1).

Risks for All-Cause Mortality

For the entire lean cohort, the median follow-up was 229 months, while for the lean NAFLD cohort, it was 214 months. The weighted unadjusted all-cause mortality was significantly higher in the lean NAFLD group than in lean control subjects without NAFLD (40.9 vs. 17.9%, P <0.001). The unadjusted hazard ratio (HR) for all-cause mortality in lean NAFLD patients was 2.44 (95% CI 1.77–3.37). Even after adjusting for demographic variables, metabolic components, and primary comorbidities, NAFLD remained independently associated with increased risk of all-cause mortality (adjusted HR 1.54, 95% CI 1.25–1.89) (Figure 2). Additionally, older age, male sex, being a smoker, presence of diabetes/IR, having high cholesterol, CKD, CVD, and emphysema were all associated with increased mortality (Table 2).

Risks for CV Mortality

The weighted unadjusted CV mortality was also significantly higher in lean NAFLD subjects than in lean control subjects without NAFLD (15.1 vs. 3.7%, P <0.001) (Table 1). The unadjusted HR for CV morality in the lean NAFLD group was 4.83 (95% CI 3.44–6.79). After adjusting for demographic variables, metabolic components, and primary comorbidities, NAFLD was statistically associated with increased risk of CV mortality (adjusted HR 2.38, 95% CI 1.50–3.77) (Figure 3). Again, older age, male sex, being a smoker, CKD, and CVD were associated with increased CV mortality (Table 2).

Discussion

The reciprocal association between NAFLD and obesity has been con-

TABLE 1. Characteristics of Participants by NAFLD Status Among Lean Individuals, NHANES III (1988–1994)

Characteristics	*N*	All (Weighted) *n* = 5,375	No NAFLD (Weighted) *n* = 4,794	NAFLD (Weighted) *n* = 581	*P*
Age, years	5,375	42.56 ± 0.60	41.8 ± 0.60	50.92 ± 1.26	<0.0001
Age, %					
20–44 years		64.23 ± 1.49	66.17 ± 1.52	42.72 ± 3.12	<0.0001
45–54 years		11.55 ± 0.72	11.32 ± 0.73	14.11 ± 2.71	0.2677
55–64 years		9.22 ± 0.61	8.60 ± 0.64	16.07 ± 2.68	0.0011
≥65 years		15.00 ± 1.12	13.91 ± 1.11	27.10 ± 2.72	<0.0001
Male, %	5,375	40.80 ± 0.75	39.19 ± 0.86	58.67 ± 3.13	<0.0001
Race, %	5,375				
White		79.24 ± 1.44	80.36 ± 1.45	66.78 ± 3.22	<0.0001
Black		8.28 ± 0.65	8.33 ± 0.68	7.82 ± 1.05	0.6663
Mexican		4.01 ± 0.38	3.82 ± 0.38	6.04 ± 0.76	0.0002
Other		8.47 ± 0.96	7.49 ± 0.96	19.36 ± 2.85	<0.0001
Income (PIR), %	4,925	3.19 ± 0.07	3.23 ± 0.07	2.80 ± 0.16	0.0071
Low (PIR <1.3)		17.06 ± 1.27	16.56 ± 1.23	22.77 ± 2.75	0.0024
Middle (PIR 1.3 to <3.5)		44.16 ± 1.48	43.74 ± 1.48	48.96 ± 3.50	0.1131
High (PIR ≥3.5)		38.78 ± 1.63	39.71 ± 1.63	28.27 ± 3.53	0.0013
Health, reported, %	5,373				
Excellent/very good		59.19 ± 1.58	60.72 ± 1.53	42.22 ± 4.04	<0.0001
Good		29.05 ± 1.06	28.63 ± 1.11	33.67 ± 2.79	0.0752
Fair/poor		11.76 ± 0.80	10.64 ± 0.77	24.11 ± 2.57	<0.0001
Smoker, %	5,373	32.43 ± 1.09	32.81 ± 1.12	28.29 ± 2.81	0.1218
Comorbidities, %					
Diabetes with IR	5,371	1.94 ± 0.24	0.29 ± 0.11	20.28 ± 2.27	<0.0001
High cholesterol	5,374	14.99 ± 0.74	13.19 ± 0.74	35.03 ± 2.52	<0.0001
Hypertension	5,375	14.78 ± 0.81	13.29 ± 0.80	31.29 ± 2.59	<0.0001
Metabolic syndrome	4,724	7.96 ± 0.49	5.32 ± 0.42	43.93 ± 3.59	<0.0001
Cancer	5,375	8.26 ± 0.66	8.15 ± 0.65	9.43 ± 2.02	0.4862
CKD	5,239	9.08 ± 0.53	8.36 ± 0.56	17.26 ± 2.32	<0.0001
CVD	5,375	3.91 ± 0.47	3.36 ± 0.41	10.03 ± 1.59	<0.0001
Emphysema	5,373	2.36 ± 0.24	2.30 ± 0.25	3.03 ± 0.60	0.1949
All-cause mortality	5,375	19.81 ± 1.03	17.91 ± 0.93	40.92 ± 3.26	<0.0001
CV mortality	5,362	4.63 ± 0.44	3.68 ± 0.37	15.13 ± 2.23	<0.0001

Data are presented as the mean or percentage ± standard error; N *= number of NHANES III participants.*

sistently reported (25–31). In this context, most NAFLD subjects are overweight/obese and have other components of metabolic syndrome (32–35). Despite this strong association with obesity, there are increasing data that a proportion of subjects with NAFLD are lean (12,36). In the United States, the prevalence of lean NAFLD in the general population has been estimated to be ~7% (36). In contrast, the prevalence of lean NAFLD is significantly higher in countries such as India and Korea (13,29,30,37–45). Although the presence of NAFLD in lean individuals is well documented, the clinical implications of having lean NAFLD are less clear. In a few studies with liver biopsy, significant numbers of these lean NAFLD patients had underlying NASH and advanced fibrosis (46–48). Nevertheless, data regarding the long-term mortality outcomes are quite

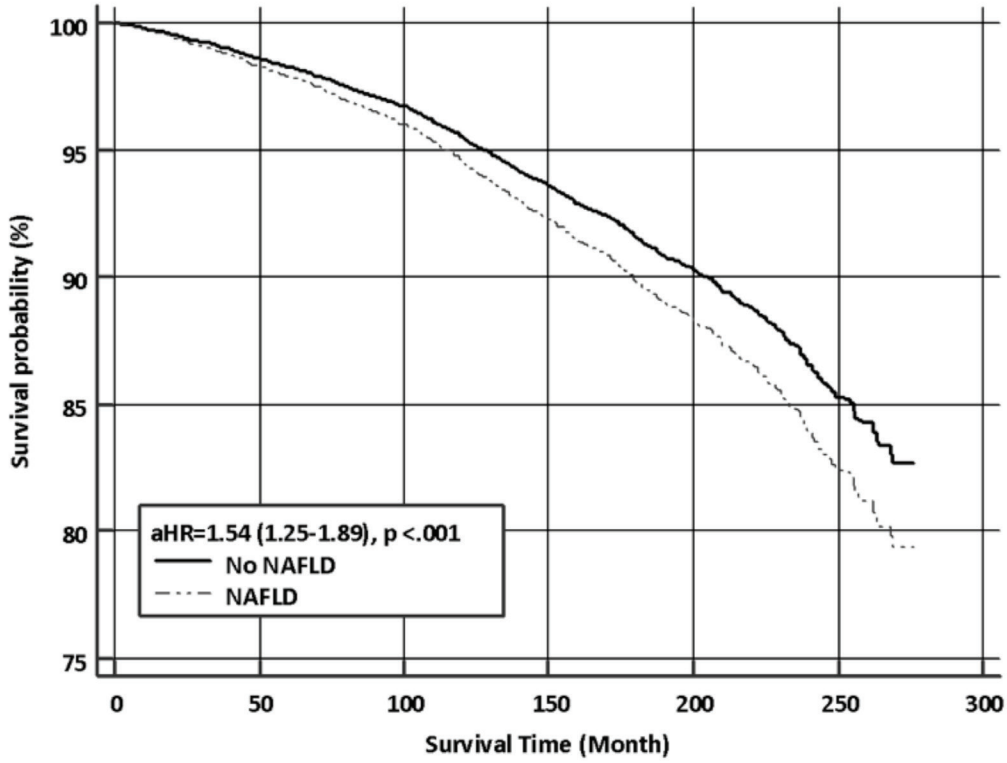

FIGURE 2. Adjusted survival curves on Cox proportion hazards model for all-cause mortality among lean individuals, NHANES III (1988–1994). aHR, adjusted HR.

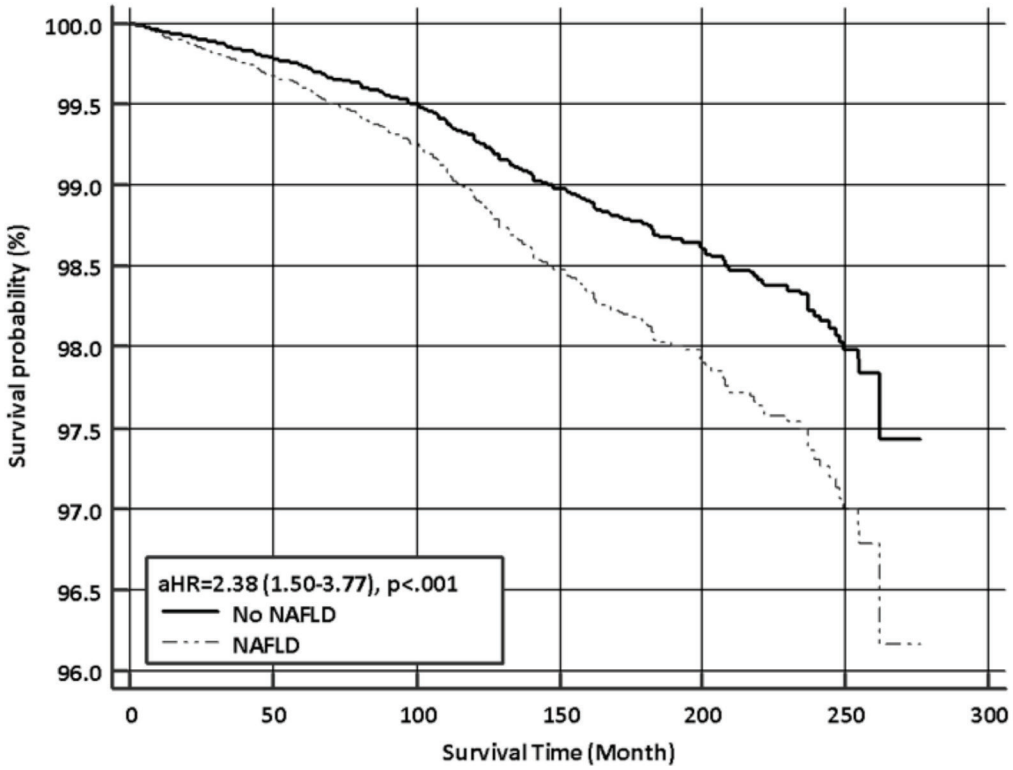

FIGURE 3. Adjusted survival curves on Cox proportion hazards model for cardiovascular mortality among lean individuals, NHANES III (1988–1994). aHR, adjusted HR.

TABLE 2. Independent Predictors of All-Cause and CVD Mortality Among Lean Individuals, NHANES III (1988–1994)

	All-Cause Mortality HR (95% CI)	*P*	CVD mortality HR (95% CI)	*P*
Lean NAFLD	1.54 (1.25–1.89)	0.0002	2.38 (1.50–3.77)	0.0004
Age, years		<0.0001		<0.0001
20–44	Reference		Reference	
45–54	3.97 (2.51–6.29)	<0.0001	4.69 (1.44–15.21)	0.0112
55–64	10.85 (7.40–15.91)	<0.0001	14.63 (4.46–48.02)	<0.0001
≥65	37.29 (26.83–51.81)	<0.0001	58.99 (20.24–171.93)	<0.0001
Male	1.43 (1.24–1.65)	<0.0001	1.80 (1.42–2.28)	<0.0001
Race		0.0020		0.0356
White	Reference		Reference	
Black	1.12 (0.92–1.37)	0.2627	0.81 (0.55–1.20)	0.2824
Mexican	0.75 (0.60–0.94)	0.0140	0.49 (0.31–0.78)	0.0034
Other	0.59 (0.39–0.88)	0.0107	0.67 (0.32–1.39)	0.2710
Income (PIR)		0.0001		0.0311
Low (PIR <1.3)	Reference		Reference	
Middle (PIR 1.3 to <3.5)	0.68 (0.56–0.83)	0.0003	0.59 (0.38–0.90)	0.0162
High (PIR ≥3.5)	0.57 (0.45–0.73)	<0.0001	0.55 (0.34–0.88)	0.0149
Smoker	1.76 (1.48–2.09)	<0.0001	1.68 (1.09–2.58)	0.0193
Comorbidities				
Diabetes/IR	1.35 (1.04–1.75)	0.0269	1.64 (0.95–2.82)	0.0738
Hypertension	0.90 (0.77–1.06)	0.2136	1.05 (0.72–1.55)	0.7872
High cholesterol	1.36 (1.11–1.65)	0.0032	1.37 (0.96–1.95)	0.0810
Cancer	1.13 (0.93–1.36)	0.2131	1.00 (0.74–1.34)	0.9717
CKD	2.05 (1.70–2.46)	<0.0001	2.71 (1.97–3.73)	<0.0001
CVD	1.69 (1.35–2.11)	<0.0001	2.76 (2.02–3.77)	<0.0001
Emphysema	1.93 (1.36–2.75)	0.0004	1.28 (0.68–2.42)	0.4410

scarce. In one study with 49 months of follow-up, mortality rates were not different between the obese and lean NAFLD patients, with CV events being the most important outcomes (48).

In the context of long-term outcomes, our study highlights a number of important issues. First, compared with lean controls, lean NAFLD patients had significantly higher rates of diabetes, hypertension, and IR. This indicates that presence of fatty liver is a surrogate for underlying metabolic abnormality, even in the absence of obesity. Furthermore, the prevalence of CV conditions, which are the major cause of mortality among patients with NAFLD, was significantly higher in the lean NAFLD group than in lean control subjects. In these contexts, our findings are in agreement with previously published data about lean NAFLD (29–31). Although the prevalence of these metabolic conditions is higher in the lean NAFLD patients than in the lean control subjects, it has previously been shown that these rates are still lower than the rates for obese NAFLD patients (36). In this context, it is plausible that there is spectrum of metabolic abnormality, with obese NAFLD subjects having the most abnormal metabolic profile, whereas lean control subjects without NAFLD have the best metabolic profile, and lean individuals with NAFLD fall somewhere in between (29,31,32,36). This indicates that although the exact prevalence rates of lean NAFLD may vary according to the geographic areas of the world, most lean NAFLD subjects will have some degree of metabolic abnormality.

The most important aspect of our study was the long-term outcomes of patients with lean NAFLD. In this study, we show that even after controlling for all important confounders, having lean NAFLD is associated with both increased overall mortality and CV mortality. These data indicate that NAFLD in lean individuals is independently associated with mortality, especially from the CV causes. These data have important implica-

tions with documentation of fatty liver, which by itself independently increases the risk of CV mortality and overall mortality. These individuals should be counseled about the risk, and lean NAFLD should be considered like any other risk for adverse CV outcomes and managed accordingly.

This study does have some limitations. First, we used ION and its validation by ultrasound as the diagnostic strategy for NAFLD. It is possible that some patients with NAFLD were not picked up by ultrasound or ION, which underestimates the true impact of NAFLD in the lean population. Additionally, CVD history was obtained from self-reported medical history in the NHANES studies, which could cause a reliability issue in the absence of qualitative and quantitative data. Similarly, alcohol consumption was determined by self-report, which has moderate reliability in active drinkers and high reliability among nondrinkers.

In conclusion, this study revealed that lean individuals with NAFLD have metabolic abnormality as documented by higher rates of components of metabolic syndrome, which, in turn, puts them at increased risk for CV and all-cause mortality. In this context, the presence of fatty liver should prompt clinicians to address metabolic conditions that may potentially modify the long-term outcomes in these individuals, regardless of their body weight.

Duality of Interest

Z.M.Y. is a consultant to Bristol-Myers Squibb, Gilead, AbbVie, Intercept, and GlaxoSmithKline. No other potential conflicts of interest relevant to this article were reported.

Author Contributions

P.G., N.F., C.T.L., and L.d.A. participated in the study design and helped with the interpretation of the data and drafting of the manuscript. J.P. performed the statistical analysis and helped with the interpretation of the data. Z.M.Y. conceived of the study, participated substantially in its design and coordination, and helped draft the manuscript. All authors read and approved the final manuscript. Z.M.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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