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Original Article

Differential Mortality Outcomes in Real-world Patients with Lean, Nonobese, and Obese Nonalcoholic Fatty Liver Disease

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Abstract

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is commonly associated with obesity but can develop in normal-weight people (lean NAFLD). We compared outcomes in lean, overweight, and obese NAFLD. ***Methods:*** This retrospective chart review included patients at Stanford University Medical Center with NAFLD confirmed by imaging between March 1995 and December 2021. Lean, overweight, and obese patients had body mass index of <25.0, >25.0 and <29.9, and ≥30.0 kg/m^2 for non-Asian and >23.0 and ≥27.5 for overweight and obese Asian patients. ***Results:*** A total of 9061 lean (10.2%), overweight (31.7%), and obese (58.1%) patients were included. Lean patients were 5 years older than obese patients (53±17.4 vs. 48.7±15.1 years), more were female (59.6% vs. 55.2%), white (49.1% vs. 46.5%), had NASH (29.2% vs. 22.5%), cirrhosis (25.3% vs.19.2%), or nonliver cancer (25.3% vs. 18.3%). Fewer had diabetes (21.7% vs. 35.8%) or metabolic comorbidities (all p<0.0001). Lean NAFLD patients had liver-related mortality similar to other groups but higher overall (p=0.01) and nonliver-related (p=0.02) mortality. After multivariable model adjustment for covariates, differences between lean and obese NAFLD in liver-related, nonliver-related, and overall mortality (adjusted hazard ratios of 1.34, 1.00, and 1.32; p=0.66, 0.99, and 0.20, respectively) were not significant. ***Conclusions:*** Lean NAFLD had fewer metabolic comorbidities but similar adverse or worse outcomes, suggesting that it is not benign. Healthcare providers should provide the same level of care and intervention as for overweight and obese NAFLD.

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Keywords: Chronic liver disease; Cirrhosis; Lean NAFLD; Liver-related mortality; NAFLD; NASH; Nonliver cancer mortality.

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CLD, chronic liver disease; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NDI, National Death Index; T2DM, type 2 diabetes mellitus.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) has become one of the most prevalent chronic liver diseases (CLDs) in the USA, most likely as a result of the increasing rates of obesity and type 2 diabetes mellitus.[1] Approximately 20% of patients with NAFLD can progress to nonalcoholic steatohepatitis (NASH) with fibrosis, cirrhosis requiring liver transplantation, or death. In addition, the presence of NAFLD is associated with decreased health-related quality of life and increased healthcare resource utilization, especially among those with advanced disease.

Although NAFLD is largely associated with obesity, recent studies have demonstrated that it is actually the presence of metabolic abnormalities such as high triglycerides and insulin resistance that leads to the development of fatty liver regardless of the presence of obesity. As such, NAFLD can be diagnosed in those with a normal body mass index (BMI), commonly referred to as lean NAFLD. In fact, up to 40% of persons with NAFLD can be considered nonobese and 19.2% lean, and the prevalence of lean NAFLD is approximately 5–10% in the general population.[2–4] Furthermore, lean NAFLD may have metabolic abnormalities similar to those with obese NAFLD albeit at a lower frequency and may have a higher risk for adverse outcomes, including death.[5,6]

However, others have suggested that those with lean NAFLD are at a lower risk for adverse outcomes, given their lower rate of metabolic abnormalities.[7–12] As such, some may believe that those who are lean may not warrant further or intensive diagnostic workup and/or intervention. Hindering this interpretation is that many of these studies were conducted at specialized liver practices from tertiary care institutions where selection bias may be present, whereby those with lean NAFLD appear to be at lower risk.[13] Therefore, to help address this gap in our knowledge, we aimed to use data from clinical practice to determine the long-term outcomes of patients with NAFLD who were considered lean, overweight, or obese by body mass index.

Methods

Study design and study population

This was a retrospective cohort study of consecutive patients with imaging-confirmed NAFLD who presented at any clinic at Stanford Healthcare between 1 March 1995, and 31 December 2021. Stanford Healthcare provides care for patients in Northern California at a university hospital, a community hospital, and ambulatory clinics throughout the San Francisco Bay Area. All patients had hepatic steatosis on at least one imaging report (abdominal ultrasound, computed tomography, and magnetic resonance imaging). Patients with significant alcohol use or other concurrent liver diseases such as viral hepatitis, autoimmune, or other metabolic liver disease were identified using International Classification of Diseases (ICD) codes and manual chart review of relevant laboratory and clinical records, were excluded from the analysis. The study was approved by the Institutional Review Board at Stanford University, Stanford, CA, USA.

We classified weight categories for non-Asian patients as a BMI of <25.0, ≥25.0 and ≤29.9, and ≥30.0 kg/m^2 as lean, overweight, and obese, respectively. For Asian patients, the cutoffs for overweight and obesity were >23.0 and ≥27.5 kg/m^2, respectively.[14] We defined NASH with the presence of ≥5% hepatic steatosis with inflammation and hepatocyte injury (ballooning) as per the American Association for the Study of Liver Diseases guidelines in patients who had liver biopsy.[15] For those without liver biopsy, using the presence of liver fibrosis as a surrogate of chronic inflammation and injury, we considered patients who had NAFLD and at least stage 1 liver fibrosis by noninvasive tests to have had NASH. Cirrhosis was diagnosis by the presence of at least one ICD code for cirrhosis plus the presence of cirrhosis via liver histology or noninvasive methods (stage 4 by FibroSure, FIB-4>3.25, stage 4 on shear wave ultrasound, FibroScan kPa>14, or magnetic resonance elastography kPa>4.6), or the presence of nodular liver contour or ascites on imaging, platelet count of <120,000/μL, or by clinical diagnosis of portal hypertension, ascites, or hepatic encephalopathy.

Patients were followed from first presentation with confirmed NAFLD to death, loss to follow-up, or end of the study period, whichever came first. Mortality data, including the cause of death were obtained by manual chart review and supplemented by a National Death Index search.[16] Cause of death was classified as overall mortality or cause-specific mortality, including liver-related, cardiovascular-related, cancer-related, or other. The cause of death was determined either by the National Death Index (NDI) using the NDI-established algorithm or by data from individual patient chart review, where liver-related death was assigned only when it was directly caused by a liver condition.

Statistical analysis

Values were expressed as means±SD or number and percentage (%). We used the chi-square test to compare categorical variables and the Wilcoxon rank-sum test or Kruskal-Wallis test to compare continuous variables between two or multiple groups. Student *t*-tests or analysis of variance were performed to compare the distribution of continuous variables as applicable. The primary study outcomes were NASH incidence, cirrhosis incidence, and overall mortality using the Kaplan-Meier method. We compared the rates of each of these three outcomes in lean, overweight, and obese groups using the log-rank test. We performed univariable and multivariable Cox proportional hazards regression to estimate unadjusted (HR) and adjusted hazard ratios (aHR) relating weight categories to the outcome of NASH or cirrhosis development and mortality, adjusting for factors previously reported to be potential confounders or factors with univariable *p*-values <0.10. The proportional hazards assumption was assessed using a graphical comparison between observed Kaplan-Meier survival curves with Cox-predicted curves for the same variable. We performed subgroup analysis for liver-related and nonliver-related deaths. We also performed sensitivity analyses of NASH, cirrhosis, and mortality rates, comparing the lean vs. the combined overweight and obese group. Additionally, we performed univariable and multivariable logistic regression to identify factors associated with lean NAFLD. The statistical analysis was done with Stata version 17 (Stata Corporation, College Station, TX, USA). Two-sided *p*-values <0.05 were considered statistically significant.

Results

Study population and characteristics

We identified a total of 10,207 patients with NAFLD confirmed by the presence of fatty liver on imaging. Of these, 9,061 patients had available BMIs and were included in our study analysis and categorized by BMI as lean (928, 10.2%), overweight (2,872, 31.7%), and obese (5,261, 58.1%). As shown in Table 1, there were several differences in baseline characteristics among the three study groups. Lean patients were, on average, 5 years older than obese patients, with a mean age of 53.7±17.4 years compared with overweight and obese patients (51.8±15.5 and 48.7±15.1, respectively, $p<0.0001$). There were also higher percentages of female or Asian patients in the lean group and higher percentages of male and Hispanic patients in the obese group. In the lean cohort, 30% were Asian, and 20% were Hispanic. In contrast, in the obese group, about 30% were Hispanic, and 20% were Asian.

At presentation, the lean cohort was more likely to have NASH (29.2%) or cirrhosis (25.3%) than the overweight (24.1% and 20.7%, respectively) or obese groups and (22.5% and 19.2%, respectively) ($p<0.0001$). The lean cohort was also more likely to have nonliver cancer (25.3%) than the overweight and obese groups (18%, $p<0.0001$). In contrast, the overweight and obese cohorts were more likely to have metabolic diseases such as diabetes mellitus, hypertension, and hyperlipidemia. About one in three obese patients (35.8%) had diabetes compared with one in five lean patients (21.7%). When comparing the characteristics of lean and nonlean (overweight plus obese) patients in our sensitivity analysis, we found similar patterns (Supplementary Table 1). In multivariable logistic regression analysis (Supplementary Table 2), we found older age (adjusted odds ratio [aOR]: 1.03, 95% confidence interval. [CI]: 1.02–1.03, $p<0.0001$) and Asian group (aOR: 1.22, 95% CI: 1.03–1.45, $p=0.02$) were significantly associated with having lean NAFLD, while being male, Hispanic, and having diabetes mellitus, hypertension, and hyperlipidemia were associated with lower odds of having lean NAFLD.

Risk of NASH and cirrhosis development in NAFLD patients by weight category

A total of 95 lean patients over a follow-up of 27,013 persons-year, 292 overweight patients over 90,815 persons-years, and 638 obese patients over 174,766 persons-years developed NASH, but there were no statistically significant differences among the three groups ($p=0.20$, Fig. 1A). The 5-year and 10-year cumulative risk of NASH development were 18.4% and 24.0% for the lean group, 15.9% and 23.2% for the overweight group, and 18.1% and 29.8% for the obese

Table 1. Patient characteristics of NAFLD patients by baseline weight category[a]

Parameter	Lean, *n*=928	Overweight, *n*=2,872	Obese, *n*=5,261	*p*-value
Mean age±SD	53.7±17.4	51.8±15.5	48.7±15.1	<0.0001
Sex				<0.0001
Female, %	59.6	45.2	55.2	
Male, %	40.4	54.8	44.8	
Race and ethnicity				<0.0001
White	49.1	41.1	46.5	
Black	1.9	1.5	2.7	
Hispanic	19.5	23.7	29.6	
Asian	29.5	33.7	21.2	
Mean BMI±SD	22.3±2.0	27.0±1.8	35.9±6.3	<0.0001
Cirrhosis	25.3	20.7	19.2	<0.0001
NASH	29.2	24.1	22.5	<0.0001
Mean FIB-4 index±SD	2.4±9.3	1.4±2.2	1.4±3.8	<0.0001
Mean ALT±SD	69.6±255.4	66.3±111.1	73.1±160.8	<0.0001
Mean AST±SD	54.7±163.0	52.5±216.8	54.2±246.1	0.001
Mean total bilirubin±SD	0.8±1.2	0.7±0.6	0.6±0.8	0.0001
Mean platelet±SD	241.7±86.6	247.8±81.5	255.5±81.7	<0.0001
Mean creatinine±SD	0.9±0.4	0.9±0.4	0.9±0.5	0.0001
Diabetes mellitus, %	21.7	23.9	35.8	<0.0001
Hypertension, %	35.1	40.3	48.2	<0.0001
Hyperlipidemia, %	41.4	50.5	47.8	<0.0001
Cardiovascular diseases, %	8.7	7.3	8.9	0.04
Chronic kidney disease, %	22.2	22.7	24.7	0.07
Nonliver cancer, %	25.3	18.9	18.3	<0.0001

[a]Weight category by BMI (kg/m^2): lean, <25; overweight, 25 to <29.9, and obese, ≥ 30 for non-Asian patients and adjusted cutoffs of 23 and 27.5, respectively, for Asian patients. ALT, Alanine aminotransferase; AST, Aspartate transferase; BMI, body mass index; FIB-4, fibrosis-4 index; NASH, nonalcoholic steatohepatitis; SD, standard deviation.

group. Contrary to the differences in the prevalence of cirrhosis at presentation, there were no statistically significant differences in the risk of cirrhosis among the different weight categories (p=0.22, Fig. 1B). A total of 76 cirrhosis cases developed during study follow-up in the lean group (28,416 person-years), 244 in the overweight (95,128 person-years), and 532 the obese group (181,458 person-years), yielding a 5-year and 10-year cumulative cirrhosis incidence of 13.8%

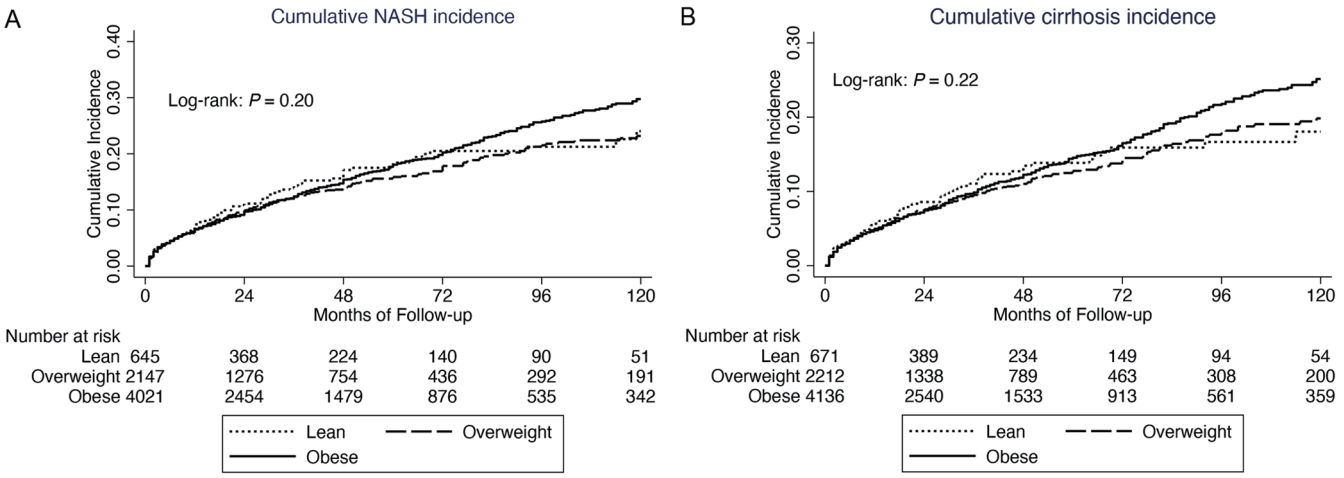

Fig. 1. Cumulative incidence of (A) nonalcoholic steatohepatitis (NASH) and (B) cirrhosis by weight category.

Table 2. Comparison of weight categories[a] and characteristics associated with NASH, cirrhosis, and mortality

Characteristic	Events, *n*	Univariable HR (95% CI)	*p*-value	Multivariable* HR (95% CI)	*p*-value
NASH					
Obese	638	1	N/A	1	N/A
Overweight	292	0.87 (0.76–1.00)	0.05	0.89 (0.77–1.03)	0.13
Lean	95	0.95 (0.77–1.18)	0.66	0.91 (0.73–1.14)	0.43
Cirrhosis					
Obese	532	1	N/A	1	N/A
Overweight	244	0.87 (0.75–1.01)	0.07	0.88 (0.76–1.04)	0.14
Lean	76	0.90 (0.71–1.14)	0.39	0.84 (0.65–1.08)	0.18
Overall mortality					
Obese	114	1	N/A	1	N/A
Overweight	66	1.11 (0.82–1.50)	0.52	1.06 (0.77–1.47)	0.70
Lean	30	1.61 (1.08–2.41)	0.02	1.32 (0.86–2.01)	0.20
Liver-related mortality					
Obese	11	1	N/A	1	N/A
Overweight	9	1.57 (0.65–3.78)	0.32	1.61 (0.65–3.98)	0.31
Lean	3	1.67 (0.47–6.00)	0.43	1.34 (0.36–4.96)	0.66
Nonliver-related mortality					
Obese	103	1	N/A	1	N/A
Overweight	57	1.06 (0.76–1.46)	0.74	1.31 (0.83–2.04)	0.24
Lean	27	1.61 (1.05–2.46)	0.03	1.00 (0.71–1.41)	0.99

[a]Weight category by BMI (kg/m^2): Lean, <25; overweight, 25 to <29.9; and obese, ≥30 for non-Asian patients and adjusted cutoffs of 23 and 27.5, respectively, for Asian patients. *Models were adjusted for age, sex, race and ethnicity, and diabetes. HR, hazard ratio; N/A, not applicable; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

and 18.1% in the lean group, 12.8% and 19.8% in the overweight group, and 14.5% and 25.1% in the obese group.

On multivariable Cox regression adjusted for age, sex, race and ethnicity, and diabetes, compared with obese NAFLD, having lean NAFLD was not independently associated with the development of NASH (aHR: 0.91, 95% CI: 0.73–1.14, p=0.43) or cirrhosis (aHR: 0.84, 95% CI: 0.65–1.08, p=0.18) (Table 2). Similar findings were observed in the sensitivity analysis comparing the lean vs. nonlean (overweight plus obese) groups, with no significant differences in the rates of NASH (p=0.99) or cirrhosis (p=0.73) development and no statistically significant difference in the risk of NASH (aHR: 0.93, 95% CI: 0.72–1.21, p=0.59) or cirrhosis (aHR: 0.88, 95% CI: 0.69–1.12, p=0.30) development in the lean and nonlean groups (Supplementary Fig. 1A, B and Supplementary Table 3).

Mortality risk in NAFLD patients by cause of death and by weight category

Overall, liver-related, and nonliver-related mortality rates by weight category: There were 30, 66, and 114 deaths over the study follow-up in person-years of 38,742, 124,085, and 237, 536 in the lean, overweight, and obese groups, respectively. Liver-related deaths accounted for 3, 9, and 11 of the deaths in lean, overweight, and obese patients, respectively. The mortality rates in the overweight and the obese group appeared to closely approximate each other throughout the 10-year study observation period for the overall as well as the subcategories of liver and nonliver-related mortality (Fig. 2A-C).

In contrast, the mortality rate of the lean group appeared to be higher than the other two groups for overall, as well as liver-related and nonliver-related mortality rates. However, the difference was only statistically significant for the comparison of overall and nonliver-related mortality (p=0.01 and p=0.02, respectively) but not liver-related mortality (p=0.71). Of note, there were only three liver-related deaths in the lean group and with the last event at month 41 into follow-up (Fig. 2B). Sensitivity analysis combining the overweight and obese group confirmed the large difference with higher overall (p=0.005) and nonliver mortality (p=0.007) in the lean compared with the nonlean group (Supplementary Fig. 2A-C).

Comparison of weight categories for association with overall, liver-related, and nonliver-related mortality: On univariable analysis, lean NAFLD was associated with a higher risk of overall (HR 1.61, 95% CI: 1.08–2.41, p=0.02) and nonliver-related (HR 1.61, 95% CI: 1.05–2.46, p=0.03) mortality (Table 2). However, on multivariable analysis adjusted for age, sex, race, ethnicity, and diabetes, lean NAFLD was not independently associated with overall (aHR: 1.07, 95% CI: 0.77–1.47, p=0.20), liver-related (aHR: 1.34, 95% CI: 0.36–4.96, p=0.66) or nonliver-related (aHR: 1.00, 95% CI: 0.71–1.41, p=0.99) mortality compared with obese NAFLD. The findings were consistent with the results of sensitivity analysis comparing lean NAFLD with nonlean mortality in the combined overweight and obese NAFLD group (Supplementary Table 3).

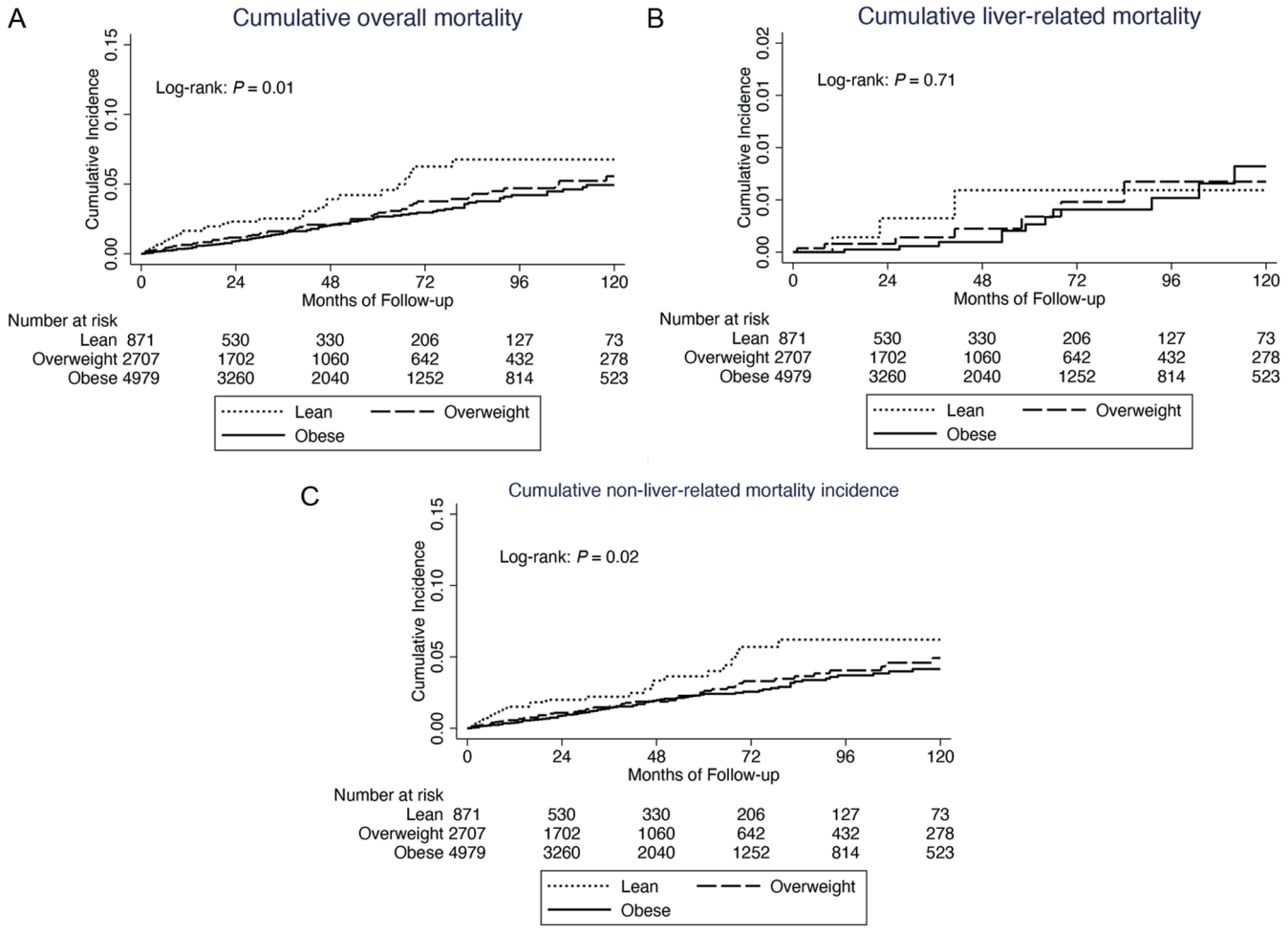

Fig. 2. Cumulative incidence of (A) overall, (B) liver-related, and (C) nonliver-related mortality by weight category.

Discussion

Using data from routine clinical practice, we determined the long-term outcomes of patients with NAFLD who were considered lean, overweight, or obese by their BMI. In this large cohort of patients, we found that lean NAFLD patients were less likely to have metabolic disease compared to other groups. In fact, obese patients had more diabetes mellitus and other metabolic diseases than those with lean NAFLD, as also seen in a recent meta-analysis on lean NAFLD.[17] Those with lean NAFLD also did not have a lower risk of liver events than those with a higher BMI. On the other hand, lean NAFLD did have higher overall and nonliver-related mortality. The cumulative 10-year mortality incidence for overall and nonliver-related NAFLD was also significantly higher in those with lean NAFLD compared with those who were overweight or obese. However, given that the lean group was significantly older than the other groups, the increase in mortality was most likely associated with age, which is what we found in our multivariate model where after controlling for age, being lean was no longer independently associated with mortality. These findings held in our sensitivity analysis, where we compared lean to the combined nonlean group of overweight and obese patients.

Our results are similar to another population-based study conducted in the USA in Olmsted County.[18] In fact, the percent of lean NAFLD among their study population was similar to ours (8.5% vs. 10.2%, respectively), as well as the demographic and clinical characteristics where those lean were most frequently female and white with a lower prevalence of metabolic comorbidities and no difference in adverse outcomes of NASH, cirrhosis, or mortality after adjusting for covariates of age, sex, race and ethnicity, and diabetes mellitus. The use of NHANES data produced similar results as ours, including mortality.[19] A recent meta-analysis from Japan using individual patient-level data, like our study, also showed that persons with lean NAFLD were older and had a higher all-cause mortality rate; however, as in our study, once age and other covariates were controlled for, lean NAFLD was not associated with increased risk of all-cause mortality.[3]

Other studies found results that were different from ours.[7–12] Investigators of a study from Hong Kong and China found that those with nonobese NAFLD were at a higher risk for mortality.[8] Although the patient population for their nonobese cohort was similar to our lean cohort in that they were older and more likely female, the major difference was the high rate of comorbidities, especially the presence of type 2 diabetes mellitus (T2DM) where over 50% had T2DM which was significantly higher than any of our study cohorts (all <30%). As has been reported, the presence of T2DM increases the risk of mortality among all groups exponentially,

most likely due to its very close association with the development and progression of fibrosis, the most important predictor of mortality.[9–12,20]

Taken together, this study provides further evidence for the discussion that describing NAFLD as the liver manifestation of metabolic syndrome for those with lean NAFLD may not be appropriate.[13] As has been pointed out above, the number of metabolic comorbidities as part of metabolic syndrome present in lean NAFLD is significantly less than in those overweight and obese. As such, although the pathophysiology for the development of lean NAFLD, including the role of sarcopenia and the presence of visceral obesity, remains to be completely unraveled, it does appear that despite the metabolic differences, lean NAFLD is not a benign condition and carries significant risk for advanced liver disease, nonliver cancers, and cardiovascular disease.[6,21]

In fact, a recent study investigated the hospitalization trends for those with lean/nonobese NAFLD compared to obese NAFLD using the US National Inpatient Sample database.[22] They determined that over the 5-year span of their study, the hospitalization rate increased yearly among the lean/nonobese as compared to the obese NAFLD population. The lean NAFLD population was also older and had fewer metabolic comorbidities but were more likely to have cirrhosis, decompensated cirrhosis, and die. Therefore, those with lean NAFLD should be monitored and treated at the same level as those with overweight or obese NAFLD.

There are many strengths of this study. Our study population included patients seen in all clinics at our medical center, most of whom were not specialized liver clinics, so our results can be more generalizable to the adult population. This is further supported by our finding that the lean population makes up almost 11% of the NAFLD population which is in line with the reported prevalence of lean NAFLD from large systematic reviews and meta-analytic data (2). Our sample size was almost double that of the other population-based study in Olmstead County, MN, and with more racial and ethnic diversity.[18] The diagnosis of NAFLD was confirmed by imaging and chart review. In addition, while further supplementing our mortality data obtained from medical record review at our medical center can help capture death data more thoroughly, reliance on the NDI for death data may also have created a misclassification of the cause of death resulting in an under reporting of liver-related mortality. However, the NDI uses a complex algorithm to determine the primary cause of death, so if there was an underreporting, it was consistent across all groups. We also acknowledge that the operational definition of NASH in patients without liver biopsy used in our study was liberal and could have underestimated the presence of NASH. However, as most real-world NAFLD patients do not undergo liver biopsy, focusing only on biopsy patients may also introduce significant selection bias. The number of events, especially for liver-related death was also small and a lower BMI can also occur in patients with cancer in general, and liver-specific death data should be interpreted with caution although our data are consistent with prior reports of nonliver causes as the major causes of death rather than liver-related causes in people with NAFLD.[6]

Conclusion

Although NAFLD is mainly thought of as a liver disease in those who are overweight and obese, it also occurs in normal-weight individuals. In our study, we found that those with lean NAFLD tended to be older and female with fewer metabolic comorbidities but with advanced liver disease and NASH. In addition, almost 10% had cardiovascular disease, a rate similar to those with obese NAFLD, while over a quarter had nonliver cancer, a rate higher than in the overweight or obese NAFLD groups. Those with lean NAFLD also had a higher rate of all-cause and nonliver-related mortality, but after controlling for age and other comorbidities, a lean BMI was not an independent predictor of mortality. Taken together, lean NAFLD is not benign. Therefore, healthcare providers should provide the same level of care and intervention as for those with overweight and obese NAFLD.

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None to declare.

Conflict of interest

MHN: Research funding: Pfizer, Enanta, Gilead, CurveBio, Exact Sciences, Helio Health, Glycotest, National Cancer Institute, B.K. Kee Foundation, Vir Biotech; Consulting: Gilead, Intercept, GSK, Exact Science, Novartis, Janssen, Bayer. RC: Research funding: Gilead, Siemen Healthineers. The other authors have no conflict of interests related to this publication.

Author contributions

Study design (VHN, MHN), data analysis (VN, SB, MN), data collection (all authors), drafting of manuscript (VHN, MHN), data interpretation, review, and revision of manuscript (all authors).

Ethical statement

This study was carried out in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board at Stanford University, Stanford, CA, USA. The individual consent for this retrospective study was waived.

Data sharing statement

No additional data are available.

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