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# Epidemiology and prevalence of lean nonalcoholic fatty liver disease and associated cirrhosis, hepatocellular carcinoma, and cardiovascular outcomes in the United States: a population-based study and review of literature

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**Ethical approval:** IRB approval was waived for this study as it was done by retrospective analysis of de-identified data from a HIPAA-compliant platform (Explorys Inc).
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## Abstract

**Backgrounds:** Nonalcoholic fatty liver disease (NAFLD) is linked to obesity and metabolic syndrome conditions. However, a subset of NAFLD patients express a normal or low body mass index (lean NAFLD [L-NAFLD]). Our aim is to compare the prevalence of L-NAFLD to the obesity-associated NAFLD in the United States by assessing prevalence, potential risk factors, liver-related complications, and coronary artery disease outcomes.
**Methodology:** A multicenter database (Explorys Inc.) of >70 million patients across the United States was screened. A cohort of patients with "nonalcoholic fatty liver" between 1999 and 2021 was identified. Two sub-cohorts of NAFLD patients were identified: those with a body mass index (BMI) < 25 kg/m$^2$ (L-NAFLD) and those with a BMI > 30 kg/m$^2$ (obesity-associated NAFLD). We excluded patients with age <18 and those who have viral hepatitis, hemochromatosis, Wilson's disease, biliary cirrhosis, alcoholic liver disease, cystic fibrosis, alpha-1-antitrypsin deficiency, and autoimmune hepatitis. Multivariate analysis was performed to adjust for confounders.
**Results:** 68 892 260 individuals were screened. NAFLD prevalence was four per 100 000, and L-NAFLD prevalence was 0.6 per 100 000. Compared with those without, patients with L-NAFLD tended to be older (OR 2.16), females (OR 1.28), and smokers (OR 4.67) and of Asian race (OR 2.12). L-NAFLD patients were more likely to have acute coronary syndromes (OR 30.00) and metabolic syndrome (OR 2.31) despite the normal/low BMI. Esophageal varices and hepatocellular carcinoma risks were high in both cirrhosis patients.
**Conclusion:** This is the largest study to assess L-NAFLD prevalence in the United States. L-NAFLD are at a significantly higher risk for acute coronary syndromes, esophageal varices, and hepatocellular carcinoma.

## Introduction

Nonalcoholic fatty liver disease (NAFLD) is the accumulation of fat in hepatocytes in little to non-alcohol-consuming individuals and is currently considered as the most common cause of chronic liver disease worldwide.[1] The rise of NAFLD has become a public health concern, not only due to its increase in mortality from liver-related causes but also due to its extrahepatic associations and worsening outcomes that progressively increase with worsening NAFLD histology. Among those liver-unrelated complications, the increased risk for cardiovascular diseases including—but not limited to—coronary heart disease, cardiomyopathy, cardiac arrhythmias, and hypertension is probably the most notable.[2,3] Moreover, NAFLD is currently one of the top leading causes of liver transplantation for both end-stage liver disease and hepatocellular carcinoma (HCC).[4] Although the higher prevalence of this disease is related to obese individuals (51–81% of NAFLD patients have a body mass index [BMI] > 30),[5] patients with a BMI within the normal range (BMI 18.5–24.9) can present with NAFLD, which is known as lean NAFLD (L-NAFLD). In

older studies, the prevalence of L-NAFLD in the United States was ~9.7%. However, newer studies have shown that the overall prevalence of NAFLD was 32.3%, among which 29.7% were nonobese and ~13.6% had the lean variant of NAFLD.[6–8] Moreover, recent multinational investigations have revealed an increase in mortality in L-NAFLD patients with nonalcoholic steatohepatitis (NASH) and that patients with L-NAFLD had higher odds for abnormalities in their metabolic profiles that include metabolic syndrome, renal and liver function, and inflammatory state compared with healthy subjects.[9] These abnormalities were more severe in obese NAFLD compared with L-NAFLD, but the risk assessment for developing coronary artery disease in other studies did not show any difference between the two groups (NAFLD and L-NAFLD).[10] These findings can be explained by the relatively increased amounts of visceral adipose tissue among L-NAFLD individuals, which is metabolically more active than other adipose tissue depots.[11] Other studies have suggested that L-NAFLD patients have a higher risk for developing diabetes and a higher risk of incident cardiovascular diseases compared with overweight individuals without NAFLD.[12,13] The diagnosis of L-NAFLD is important in non-overweight individuals, and after the detection, a long-term follow-up is usually warranted. Despite all of its complications, L-NAFLD has been and is not deeply investigated in the United States. Therefore, our aim is to compare the prevalence of L-NAFLD with the obesity-associated NAFLD in the United States and assess for potential risk factors, liver-related complications, and coronary artery disease outcomes.

## Methodology

***Database.*** Our cohort's data were obtained using a validated, multicentered, and daily updated database (Explorys Inc., Cleveland, OH, USA) developed by IBM Watson Health.[14] Explorys consists of electronic health records of 26 different healthcare systems with a total of 360 hospitals and more than 70 million patients across the United States. Explorys utilizes Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT) for the definition of the diseases and pools large outpatient and inpatient deidentified data that can be formulated into numerous cohorts according to the clinical element being studied. Explorys further allows for the identification of the timeline of events in reference to the index clinical event of interest and hence the ability to study the temporal relationship between different variables. The Institutional Review Board approval is not required because Explorys is a Health Insurance Portability and Accountability Act-compliant platform.

***Patient selection.*** A retrospective cohort of patients with a SNOMED-CT diagnosis of "nonalcoholic fatty liver" between 1999 and 2021 was identified. Subsequently, two sub-cohorts of NAFLD patients were identified: those with a BMI $< 25$ kg/m$^2$ (L-NAFLD group) and those with a BMI $> 30$ kg/m$^2$ (obesity-associated NAFLD group). Our exclusion criteria were limited to patients less than 18 years old and/or those who have a diagnosis of viral hepatitis, hemochromatosis, Wilson's disease, biliary cirrhosis, alcoholic liver disease, cystic fibrosis, alpha-1-antitrypsin deficiency, and autoimmune hepatitis (Fig. 1).

***Statistical analysis.*** Statistical Package for Social Sciences (SPSS version 25, IBM Corp) was used for statistical analysis, and for all analyses, a two-sided $P$ value of $<0.05$ was considered statistically significant. Multivariate analysis was performed to adjust for multiple factors including age, sex, race, cirrhosis, HCC, acute coronary syndrome (ACS), smoking, esophageal varices, and metabolic syndrome.

## Results

The baseline characteristics of patients with L-NAFLD are shown in Table 1. Among the 68 892 260 screened individuals in the database, a total of 3410 individuals with NAFLD in the period from 1999 to 2021 were included in the final analysis. The 20-year prevalence rate of NAFLD was four per 100 000. Among those with NAFLD, 430 (~12%) had L-NAFLD, with an overall prevalence of 0.6 per 100 000. In comparison with those without, patients with L-NAFLD tended to be older than age of 65 (OR 2.16, 95% CI: 1.81–2.57), females (OR 1.28, 95% CI: 1.07–1.54), and smokers (OR 4.67, 95% CI: 3.48–6.26) and of

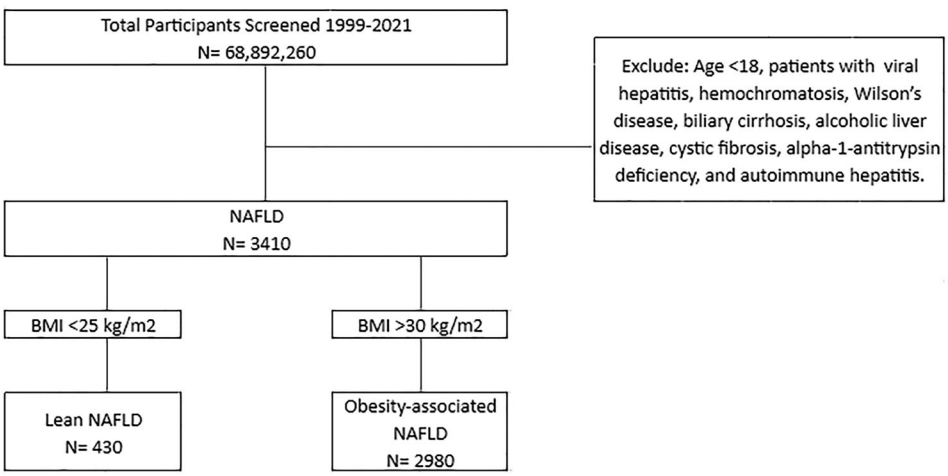


**Figure 1** Inclusion criteria and patient selection.

**Table 1** Baseline characteristics of study population

| | | Lean NAFLD (%) *N* = 430 | Obesity-associated NAFLD (%) *N* = 2980 |
|---|---|---|---|
| Age | 18–65 | 240 (55.8) | 2010 (67.4) |
| | >65 | 190 (44.2) | 970 (32.6) |
| Sex | Females | 280 (65.1) | 1670 (56.0) |
| Race | Caucasian | 360 (83.7) | 2570 (86.2) |
| | African-American | 10 (2.3) | 110 (3.7) |
| | Asian | 10 (2.3) | 40 (1.3) |
| Co-morbidities | Hypertension | 120 (27.9) | 780 (26.2) |
| | Type 2 diabetes | 150 (34.9) | 1230 (41.3) |
| | Dyslipidemia | 310 (72.1) | 2060 (69.1) |
| | Cirrhosis | 30 (7.0) | 170 (5.7) |
| | HCC | 5 (1.2) | 5 (0.2) |
| | Esophageal varices | 5 (1.2) | 50 (1.7) |
| | Ascites | 20 (4.7) | 70 (2.3) |
| Medications | Aspirin | 190 (44.2) | 1130 (37.9) |
| | Statins | 210 (48.8) | 1460 (49.0) |

Asian race (OR 2.12, 95% CI: 1.47–3.08). Interestingly, L-NAFLD patients were also more likely to have ACS (OR 30.00, 95% CI: 15.66–58.10) as well as metabolic syndrome (type 2 diabetes mellitus, hypertension, and dyslipidemia) (OR 2.31, 95% CI: 11.68–22.87) despite the normal or low BMI (Table 2). The risks for esophageal varices and HCC were high in both obesity-associated NAFLD and L-NAFLD cirrhosis patients (Table 3).

## Discussion

Over the past few decades, the prevalence of NAFLD has dramatically increased in many developed nations, contributing to an increasing socioeconomic burden on the healthcare system. We conducted one of the largest population-based study to assess L-NAFLD in the United States. Our primary aim was to compare the prevalence of L-NAFLD with obesity-associated NAFLD. A secondary aim was to evaluate the potential risk factors, liver-related complications, and CAD outcomes in the L-NAFLD population. Our study deduced that the prevalence of L-NAFLD is ~12% in the US population, concurring that L-NAFLD is not uncommon. Because an association between high BMI and

**Table 2** Multivariate analysis for obesity-associated nonalcoholic fatty liver disease and the lean variant

| | Obesity-associated NAFLD OR (95% CI) | *P* value | Lean NAFLD OR (95% CI) | *P* value |
|---|---|---|---|---|
| Age >65 | 1.1 (1.10–1.24) | 0.00 | 2.16 (1.81–2.57) | 0.00 |
| Female | 1.06 (0.98–1.19) | 0.17 | 1.28 (1.07–1.54) | 0.01 |
| Asian | 0.82 (0.613–1.06) | 0.19 | 2.12 (1.47–3.08) | 0.00 |
| Smoking | 17.71 (1.036–19.78) | 0.00 | 4.67 (3.48–6.26) | 0.00 |
| Metabolic syndrome | 8.5 (7.34–9.84) | 0.00 | 16.34 (11.68–22.87) | 0.00 |
| ACS | 11.00 (5.89–20.52) | 0.00 | 30.15 (15.66–58.10) | 0.00 |
| Cirrhosis | 6.55 (5.50–7.80) | 0 | 7.71 (5.44–10.92) | 0.00 |

**Table 3** Multivariate analysis for cirrhosis among nonalcoholic fatty liver disease and the lean variant patients

| | Obesity-associated NAFLD cirrhosis OR (95% CI) | *P* value | L-NAFLD cirrhosis OR (95% CI) | *P* value |
|---|---|---|---|---|
| Age >65 | 1.76 (1.28–2.42) | 0.00 | 1.80 (0.96–3.37) | 0.07 |
| Female | 1.44 (2.42–2.00) | 0.03 | 0.85 (0.45–1.63) | 0.63 |
| Metabolic syndrome | 2.31 (1.43–3.73) | 0.00 | 4.794 (2.00–11.47) | 0.00 |
| Varices | 27.99 (16.13–48.55) | 0.00 | 29.31 (12.77–67.33) | 0.00 |
| HCC | 20.66 (10.208–41.835) | 0.00 | 19.99 (5.80–69.05) | 0.00 |

NAFLD has been historically established, understandably, the prevalence is comparably lower than in overweight and obese individuals.[15–17]

Though the concept of L-NAFLD is relatively decades old, there have been some recent advances in regard to environmental and genetic modifiers. In a study of US population, Younossi et al. found an independent relationship between L-NAFLD and younger age, female sex, and a lower likelihood of having insulin resistance and hypercholesterolemia ($P$ values $< 0.05$). The prevalence of NAFLD was significantly lower in lean individuals than in overweight or obese individuals (7.39% ± 0.65% vs. 27.75% ± 1.00%, respectively; $P < 0.0001$).[7]

According to a recent meta-analysis, the pooled prevalence of NAFLD is 10.2% (95% CI: 7.6%–13.6%) in lean people and 15.7% (95% CI: 12.5%–19.6%) in nonobese people.[18]

Another recent meta-analysis evaluating 93 studies ($n$ = 10 576 383) from 24 countries estimated the global prevalence (10.6%) of L-NAFLD within the lean population.[19] Wang et al. reported a wider range of prevalence of 5–26% of L-NAFLD in the adult population across the globe.[20] This wide prevalence range can be explained by several factors, such as variations in study cohorts, discrepancies in the definitions, diagnostic tests for NAFLD, nutritional beliefs, and lifestyles. For instance, population studies of East Asian countries like Taiwan reported a prevalence of 11.5% *vs* 23.4% in South Korea.[21,22]

Another US-based cross-sectional study of pediatric population in which individuals enrolled in the NHANES during the 2005–2014 cycles estimated the L-NAFLD prevalence of 8% (95% CI 6.2–9.9).[23] This was a remarkable study to bring the relationship of L-NAFLD with age. The L-NAFLD subjects were significantly older than lean non-NAFLD subjects (15.5 *vs* 15 years, $P$ value $< 0.05$). These findings were similar to our illustrations. In comparison with those without, we concluded that patients with L-NAFLD tended to be older (OR 2.16). This is well reasoned in a recent meta-analysis by Ito et al., who showed that lean NAFLD individuals were older and made up 20% of the NAFLD population.[24]

Our study also demonstrated a female predilection (OR 1.28) for patients with L-NAFLD. These findings were similar to a study by Yang et al., who showed that NAFLD was more prevalent in females with lower BMI than males with lower BMI ($P < 0.001$).[25] Interestingly, L-NAFLD patients were also more likely to have metabolic syndrome (type 2 diabetes mellitus, hypertension, and dyslipidemia) (OR 2.31) despite the normal or low BMI. Several previous studies were in unison with our

conclusions. For example, Sinn et al. showed that there was an independent correlation between NAFLD and insulin resistance in middle-aged Asian adults who were nonobese and nondiabetic, irrespective of how many metabolic components were included in the metabolic syndrome (OR 3.63 [95% CI: 2.74–4.82]).[26]

Previous studies have emphasized the fact that atherogenic profile (dependent on diabetes, arterial hypertension, and dyslipidemia) is shown to be associated with NAFLD independently of BMI.[27] Kumar et al. compared the clinicopathological characteristics and metabolic profiles of NAFLD in Indian patients with normal BMI.[28] The study concluded that L-NAFLD individuals tend to have less severe diseases, have nominal insulin resistance, and be dyslipidemic, but still higher when compared with the healthy lean control subjects.

We also compared the risk of developing complications like esophageal varices and HCC in our two cohorts. We did not observe a statistically significant difference between the two arms. Both obesity-associated NAFLD and L-NAFLD cirrhosis patients were found to have a higher risk. This was contrary to the radical study investigating the long-term risk of mortality and development of severe liver disease in biopsy-proven lean NAFLD.[29] In the study, NAFLD patients with higher BMI had a higher risk for overall mortality compared with L-NAFLD. In a prospective multistaged community-based epidemiological study performed in a rural Indian population, Das et al. observed an 8.7% prevalence of NAFLD and 0.2% prevalence of cryptogenic cirrhosis in poor and nonobese individuals.[30]

Our study stands out in several aspects. First, it is a multicenter and of the largest study evaluating prevalence of L-NAFLD. This study also focuses on the detailed demographics and clinical features helping the audience to tailor the targeted population. To our knowledge, this is the first study to institute the risk of ACS in the L-NAFLD population (OR 30.00). Hence, we propose that even patients who are not obese should receive thorough risk assessment and treatment.

The American Association for the Study of Liver Disease (AASLD) recommends against routine screening for NAFLD in any population, regardless of BMI.[31] There is no doubt that nonobese NAFLD contributes to a large share of the burden of this chronic liver disease. Hence, BMI should not be regarded as a criterion to exclude NAFLD or to determine whether further testing is warranted for confirmation. It is essential to develop guidelines and studies that address these new challenges in order to discover more robust and homogeneous data on lean/nonobese NAFLD.

## Limitations

As most variables were generated using the Explorys database, there is always an argument regarding selection bias. This argument can be further extended in terms of the diagnosis of NAFLD. Earlier, we have learned that there is a varying specificity and PPV with the noninvasive diagnostic tree of NAFLD-NASH spectrum is still developing and prevalence can vary based on the diagnostic test used. In addition, BMI is a dynamic variable that depends on several other factors like free water weight, muscle mass, and visceral adiposity and hence is not an efficient resource. Last but not least, and owing to their different body fat distribution compared with other groups, the World Health Organization have proposed different cutoffs for obesity and overweight definitions in the Asian subgroups, with a BMI of 23–24.9 kg/m$^2$ considered to be overweight and BMI ≥ 30 kg/m$^2$ used to define obesity.[32] Due to the inseparable data extraction process in the Explorys database, analyzing this subgroup separately using these cutoffs was technique not plausible, and hence, the corresponding prevalence of this group is likely under-detected in our study.

***Data availability statement.*** Datasets used in this analysis can be found online on Explorys Inc. via IBM.

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