High Concordance Between Nonalcoholic Fatty Liver Disease and Metabolic Dysfunction-Associated Steatotic Liver Disease in the TARGET-NASH Real-World Cohort

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INTRODUCTION: **This study investigates the applicability of the new metabolic dysfunction-associated steatotic liver disease (MASLD) nomenclature to the real-world TARGET-NASH US adult cohort.**

METHODS: **The new MASLD/metabolic steatohepatitis nomenclature was applied to patients enrolled with pragmatic diagnoses of nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH), and NASH cirrhosis and concordance were determined between the definitions.**

RESULTS: **Approximately 99% of TARGET-NASH participants met the new MASLD diagnostic criteria. Approximately 1,484/1,541 (96.3%, kappa 0.974) nonalcoholic fatty liver patients (metabolic dysfunction-associated steatotic liver), 2,195/2,201 (99.7%, kappa 0.998) NASH patients (metabolic steatohepatitis), and 1,999/2,003 (99.8%, kappa 0.999) NASH cirrhosis patients met the new criteria.**

DISCUSSION: **The new MASLD nomenclature is highly concordant with the previous TARGET-NASH pragmatic definitions.**

KEYWORDS: NAFLD; NASH; MASLD; MASH; steatosis; nomenclature

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INTRODUCTION

In June 2023, a multisociety Delphi consensus statement was released changing the nomenclature of nonalcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD) (1). The change in nomenclature was made for a variety of reasons not limited to improved accuracy in naming and reducing stigma in patients with steatotic liver disease. There was also a slight change in diagnostic criteria, requiring at least one of five cardiometabolic criteria to meet the definition of MASLD. Such changes in nomenclature and disease state definitions may render previous research and patient cohorts established under older nomenclature challenging to interpret when the new nomenclature is applied. For this reason, an investigation into the real-world TARGET-NASH US cohort was conducted to assess the concordance of legacy definitions of nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), and NAFLD/NASH cirrhosis with the new MASLD nomenclature.

METHODS

TARGET-NASH is an ongoing pragmatic longitudinal real-world patient cohort designed to follow patients with NAFLD in routine clinical settings. The study's aim is to gain greater insights into disease natural history and the impact of therapeutic interventions, both off-label through routine clinical care, and through postmarketing surveillance of future Food and Drug Administration–approved therapies. Patients are enrolled in TARGET-NASH based on a treating physician's clinical or biopsy-proven diagnosis of NAFLD. There are no healthy control patients enrolled. Patients are categorized as having NAFL, NASH, or cirrhosis after enrollment according to previously published TARGET-NASH definitions. Study details and protocol are reported elsewhere (2). During enrollment, subjects complete surveys including an Alcohol Use Disorders Identification Test (AUDIT), scored from 0 to 40. Patients with legacy disease state definitions of NAFL, NASH, and NASH cirrhosis were compared with application of the new nomenclature and diagnostic criteria for MASL, metabolic steatohepatitis (MASH), and MASH cirrhosis, which were retrofit to the TARGET-NASH US adult cohort and modified slightly to reflect application in a real-world setting (Table 1). All participants were evaluated for any of the five metabolic criteria to satisfy a diagnosis of MASLD. Legacy disease states in the categories of NAFL, NASH, and

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Table 1. Side-by-side legacy TARGET-NASH disease state definitions for adults with new MASLD/MASH definitions (2)

Legacy NAFLD	MASLD
A diagnosis of NAFLD by treating provider through routine clinical care	At least 1 of 5: (1) BMI ≥25 kg/m^2 (23 in Asians) (2) HbA1c ≥5.7% (39 mmol/L) OR T2DM OR treatment for T2DM (3) Blood pressure ≥130/85 mm Hg OR specific antihypertensive drug treatment (4) Plasma triglycerides ≥1.70 mmol/L (150 mg/dL) OR lipid-lowering treatment (5) Plasma HDL-cholesterol ≤1.0 mmol/L (40 mg/dL) (male) and ≤1.3 mmol/L (50 mg/dL) (female) OR lipid-lowering treatment
NAFL Not meeting NASH or cirrhosis criteria	**MASL** ≥1 of the 5 metabolic criteria listed above. Does not meet MASH or cirrhosis criteria
NASH Confirmed by biopsy: Steatohepatitis by brunt OR NAS total score ≥4 Pragmatic clinical diagnosis: (Adults) ALT >19 U/L for female, >30 U/L for male AND Hepatic steatosis on biopsy or CT/US/MRI AND; ≥1 of the following: (1) BMI ≥30 (2) T2DM (HbA1c >6.5%) (3) Dyslipidemia	**MASH** Confirmed by biopsy: Steatohepatitis by brunt OR NAS total score ≥4 Pragmatic clinical diagnosis: (adults) ALT >19 U/L for female, >30 U/L for male AND; Hepatic steatosis on biopsy or CT/US/MRI AND ≥1 of the 5 metabolic criteria listed above
Cirrhosis (1) Liver biopsy with fibrosis stage = 4 OR (2) Liver biopsy with fibrosis stage = 3 and one or more secondary indicator OR (3) 2 or more secondary indicators OR (4) FibroScan LSM 12.5–15.9 kPa AND one or more secondary indicator OR (5) FibroScan LSM ≥16 kPa Secondary indicators: • Evidence of ascites on any imaging or scans • Evidence of portal hypertension on any imaging or scans • Any varices or portal gastropathy noted on EGD • Platelet count below 140 K • Cirrhosis noted as present or possible on any imaging or scans • Splenomegaly noted as present on any imaging or scans	**MASH cirrhosis** (1) Liver biopsy with fibrosis stage = 4 OR (2) Liver biopsy with fibrosis stage = 3 and one or more secondary indicator OR (3) 2 or more secondary indicators OR (4) FibroScan LSM 12.5–15.9 kPa AND one or more secondary indicator OR (5) FibroScan LSM ≥16 kPa Secondary indicators: • Evidence of ascites on any imaging or scans • Evidence of portal hypertension on any imaging or scans • Any varices or portal gastropathy noted on EGD • Platelet count below 140 K • Cirrhosis noted as present or possible on any imaging or scans • Splenomegaly noted as present on any imaging or scans AND; ≥1 of the 5 metabolic criteria listed above

ALT, alanine transaminase; BMI, body mass index; CT, computed tomography; EGD, esophagogastroduodenoscopy; LSM, liver stiffness measurement; MASL, metabolic dysfunction-associated steatotic liver; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI, magnetic resonance imaging; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; MASH, metabolic steatohepatitis; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes; US, ultrasound.

NASH cirrhosis were redefined to MASL, MASH, and MASH cirrhosis, respectively. Cohen's kappa values were calculated to find the agreement between NAFLD and MASLD definitions.

RESULTS

There were 5,745 patients in the cohort analyzed from 47 academic and 18 community practice centers across the United States. Mean age at TARGET-NASH enrollment was 57 years, and 59.3% were female. Cardiometabolic risk factors are highly prevalent in the TARGET-NASH cohort; 95% are overweight or obese, 70% have type 2 diabetes, 82% have hypertension, 72% have elevated triglyceride, and 76% have low HDL-cholesterol. Overall, 99% of TARGET-NASH participants met the new MASLD diagnostic criteria. Approximately 1,484/1,541 (96.3%, kappa 0.974) patients with NAFL met MASL criteria, 2,195/2,201 (99.7%, kappa 0.998) patients with NASH met MASH criteria, and 1,999/2,003 (99.8%, kappa 0.999) patients with cirrhosis met MASH cirrhosis criteria (Figure 1).

The 57 patients with a legacy NAFL definition who did not meet MASL criteria were due to the lack of a documented cardiometabolic criterion. Six patients did not meet MASH criteria because of slight differences in definition, e.g., dyslipidemia was used for NASH, whereas plasma triglycerides and HDL were used for MASH (Table 1). Four patients did not meet cirrhosis criteria because of the lack of a metabolic criterion (Figure 1).

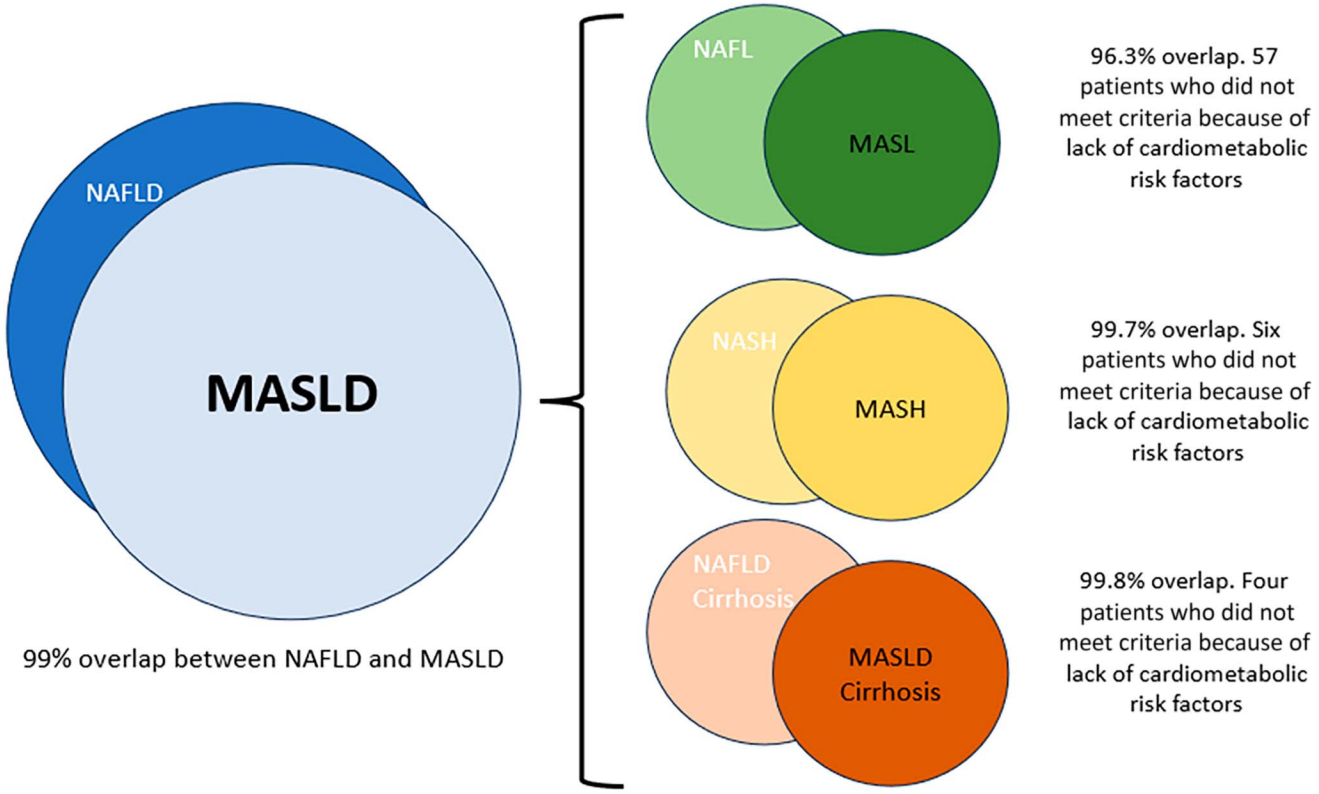

Figure 1. Venn diagram showing overlap of disease state definitions in the TARGET-NASH cohort. MASL, metabolic dysfunction-associated steatotic liver; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; MASH, metabolic steatohepatitis; NASH, nonalcoholic steatohepatitis.

In a secondary analysis, AUDIT scores (n = 4,939 questionnaires completed) were reviewed to assess alcohol use and the potential for "MASLD and increased alcohol intake" (MetALD). The median AUDIT score for all patients was 0, IQR 1 (mean 1.1, SD 2.2) (Figure 2). There was a decrease in median AUDIT score with increasing disease severity (MASL 1, MASH 1, and cirrhosis 0, $P < 0.001$). An AUDIT score of >7 was used to indicate some contribution of alcohol to hepatic steatosis and used as a surrogate for grams of alcohol intake. This revised definition showed 4,769 patients with MASLD (AUDIT ≤7 and ≥1 cardiometabolic criterion), 127 MetALD patients (AUDIT >7 and ≥1 cardiometabolic criterion), 41 cryptogenic steatosis patients (AUDIT ≤7 and no cardiometabolic criteria), and 2 ALD patients (AUDIT >7 and no cardiometabolic criteria). Based on these data, we can calculate a sensitivity range from 96.6% to 97.4%. Specificity is not calculated because of lack of healthy controls.

DISCUSSION

The pragmatic, real-world, clinical definitions for NAFL, NASH, and cirrhosis in the TARGET-NASH cohort (2,3) have been shown to be highly accurate in previous comparisons with histology interpreted by an expert histopathologist (4). The TARGET-NASH cohort pragmatic definitions are now shown to be highly accurate under the new nomenclature of MASLD and are appropriate to use for research and clinical care. These findings are consistent with other studies that have evaluated the relationship between NAFLD and MASLD definitions in different cohorts in Europe and Asia. In a study from Hong Kong by Song et al (5), of 1,016 randomly selected patients with a 25.7% prevalence of NAFLD, only 6 (2.3%) of 261 who fulfilled NAFLD criteria did not meet MASLD diagnostic criteria. Likewise, assessment of two European cohorts demonstrated high concordance in the patients described by the older nomenclature compared with the MASLD nomenclature (6,7). These TARGET-NASH data, the first from the United States, and overall largest cohort to date, show a 99% overlap with very high concordance between NAFLD and MASLD. The MASLD community should have confidence that the new nomenclature will not disrupt research on disease natural history, biomarker development, or therapeutic interventions on patients collected using the legacy definitions. For those small numbers of patients included in the

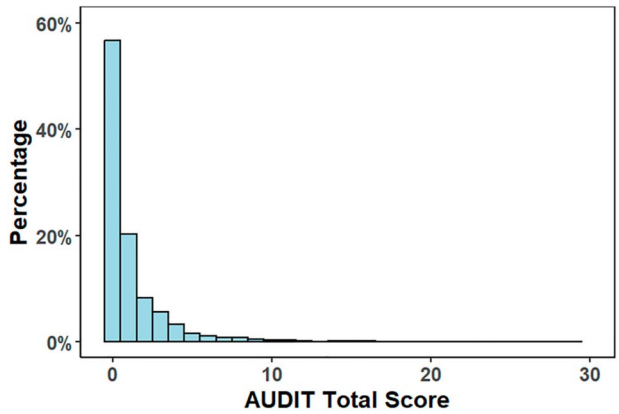

Figure 2. Alcohol Use Disorders Identification Test (AUDIT) score distribution.

TARGET-NASH cohort who did not meet MASLD diagnostic criteria, further investigation is ongoing to assess the cause of steatosis (e.g., cryptogenic vs drug-induced steatosis).

AUDIT scores >7 were used as a surrogate for alcohol use contributing to hepatic steatosis; this pragmatic definition of MetALD revealed a small but important cohort of 127 subjects who will be followed longitudinally for important cardiovascular and liver-related outcomes. As the AUDIT has not been validated as a surrogate for grams of alcohol consumed and the new MetALD nomenclature, this group will require further study.

The change in hepatic steatosis nomenclature was made for multiple reasons. Improving accuracy in disease naming by describing hepatic steatosis for what it is (metabolic), rather than by what it is not (nonalcoholic), can improve awareness and patient understanding. In addition, the field of hepatology is appropriately moving away from language that can be perceived as stigmatizing and pejorative with words such as "alcoholic" and "fatty." Some of these efforts are also seen in the newer nomenclature surrounding alcohol-induced liver disease, alcohol-associated hepatitis, and alcohol-associated cirrhosis. In a survey of 1976 patients and 825 providers across 23 countries, 47%–52% of US and South Asian patients had discomfort with the term "fatty liver disease." Similar proportions of providers believed that "nonalcoholic" was stigmatizing. The number reporting that "steatotic liver disease" was stigmatizing was low (8).

In summary, MASLD is the new NAFLD. The new nomenclature and slight alteration of disease state definitions do not render previous research irrelevant, including data collected from the TARGET-NASH cohort. Inferences made under legacy definitions may be seamlessly applied to newer studies under the new nomenclature.

CONFLICTS OF INTEREST

Guarantor of the article: A. Sidney Barritt IV, MD, MSCR, FACG.

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