Received: 24 July 2024 | Accepted: 8 August 2024

DOI: 10.1097/HC9.0000000000000546

RESEARCH LETTER

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Concordance of MASLD and NAFLD nomenclature in youth participating in the TARGET-NASH real-world cohort

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INTRODUCTION

In 2023, a multi-society Delphi consensus process led to a new nomenclature for NAFLD and NASH to be more inclusive and to redefine the disease definition to reflect the underlying pathophysiology: cardiometabolic disease.[1] Previous research findings based on the legacy terminology and definition may not be relevant to the new terminology, metabolic dysfunction–associated steatotic liver disease (MASLD)/metabolic dysfunction–associated steatohepatitis (MASH), unless high concordance can be demonstrated. To respond to this concern, the percentages of legacy-defined cases that met the criteria for the new nomenclature were analyzed in the TARGET-NASH pediatric patient cohort, similar to the analysis recently conducted on the adult cohort.[2] Concordance between the MASH pediatric definition using clinical criteria and histological diagnosis was also assessed.

METHODS

TARGET-NASH is an ongoing longitudinal observational study with over 6500 pediatric and adult patients enrolled in the United States and >6 years of median follow-up aimed at elucidating the effectiveness of therapies, both FDA-approved and off-label, within a real-world setting. Enrollment in the TARGET-NASH cohort was based on biopsy or clinical diagnosis of NAFLD. Subsequently, patients were classified into distinct categories: NAFL,

Abbreviations: MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease.

Keywords: consensus, MASLD, NAFLD

ClinicalTrials.gov Identifier: NCT02815891.

Cristian Sanchez-Torres and Ana Ramirez Tovar are co-first authors.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepcommjournal.com.

NASH, or cirrhosis, by pre-established definitions (Supplemental Table S1, http://links.lww.com/HC9/B56).[3,4] In the present analysis, pediatric patients enrolled in TARGET-NASH with the legacy phenotypes, that is, NAFL, NASH, and NASH cirrhosis, were verified with the new nomenclature requiring evidence of steatosis and at least 1 of 5 metabolic criteria, termed MASLD. NAFLD and MASLD agreement definition was determined using kappa values. For patients with available liver biopsy scanned images (N = 41), histology was overread by a central pathologist, and biopsy-defined MASH was compared to the TARGET-NASH clinical definition, similar to previous analysis in the adult cohort.[4] Sensitivity and positive predictive value were measured.

RESULTS

There were 828 pediatric patients enrolled in TARGET-NASH across 12 pediatric liver programs with research facilities and 1 community center across the United States. The mean age at enrollment was 13 (SD: 2.67, range: 4–17), and 30% were females. In the study cohort, MASLD cardiometabolic factors were widely present; 98% of participants were overweight or obese, 50% had high triglycerides or low HDL-cholesterol levels, 45% had hyperglycemia or were treated for type II diabetes, and 26% had hypertension (Supplemental Table S2, http://links.lww.com/HC9/B56). Overall, 99% of the pediatric TARGET-NASH cohort met the new MASLD definition (Table 1). Under the legacy definition, 7 patients with NAFL (2.5%) and 1 patient with NASH (0.2%) did not meet at least 1 of the 5 metabolic criteria. Of those 8, 1 did not meet any cardiometabolic criteria (body mass index percentile 80), 7 had incomplete data during the enrollment period (6 mo); however, 2 of them met the metabolic dysfunction–associated steatotic liver or MASH criteria after the enrollment period.

Twenty-eight patients with NAFL satisfied MASH criteria 6 months after enrollment. All 22 patients with NAFLD cirrhosis (100%) met at least 1 of the 5 metabolic criteria. The Cohen's Kappa coefficient for NAFL, NASH, and NASH cirrhosis was at 0.90 or higher.

Of the 41 pediatric stained biopsy slides available, 37 showed definite, probable, or possible MASH as determined by central pathology reading (Supplemental Table S3, http://links.lww.com/HC9/B56). The clinical TARGET-NASH definition of MASH identified 33 out of 37 (89.2%) biopsy-defined MASH cases (including MASH cirrhosis, N = 3) with a sensitivity of 0.89 and a positive predictive value of 0.89. Four out of 37 participants who met the clinical criteria did not meet the central pathologist diagnosis of MASH (3 with probable or possible NAFLD and 1 with suggested focal perisinusoidal fibrosis). Four out of 41 cases that met the biopsy MASH definition did not meet the MASH clinical definition (body mass index <30, no reported dyslipidemia, reported HbA1c ≤ 6.5, or no reported type 2 diabetes).

TABLE 1 Comparison of MASLD/MASH phenotypes with legacy TARGET-NASH phenotypes for patients enrolled at age 17 or younger (N = 828)

MASLD (satisfy at least 1 metabolic risk factor)	Legacy NAFLD	New MASLD/MASH	n (%)
Yes			
	NAFL	MASL	284 (34.30)
	NASH	MASH	514 (62.08)
	NAFLD cirrhosis	MASH cirrhosis	22 (2.66)
No			
	NAFL		7 (0.85)
	NASH		1 (0.12)

Note: Data cut January 26, 2024. Cohort using data before and up to 6 months after enrollment.

Abbreviations: MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease.

DISCUSSION

The Delphi consensus for new steatotic liver disease nomenclature was published at the end of 2023 to address the dependence on an exclusionary term (nonalcoholic) and to decrease stigmatization (1-delphi). The new definition also featured the inclusion of cardiometabolic factors related to the underlying pathophysiology. Of the pediatricians surveyed for the nomenclature consensus process, 55% and 60% believed the terms fatty and alcoholic, respectively, were stigmatizing.[1] This is the first pediatric study to investigate the degree of correlation between the old and new nomenclature; however, similar studies performed in adult cohorts in TARGET-NASH,[2] as well as in Hong Kong and Sweden also found high concordance. Specifically, in the Sweden cohort, of 1329 of the 1333,[5] and in the Hong Kong cohort, 255 out of the 261 adult patients fulfilled the diagnosis criteria of MASLD.[6]

Our findings demonstrate that the legacy and new disease categories have a very high level of concordance with the new MASLD/MASH terminology for children, facilitating the continued translation of research based on the legacy terminology. Furthermore, the strong concordance between the clinical definition of MASH and the study's centrally read histological interpretation offers a valuable tool for the clinical evaluation of the MASLD stage without the need for a liver biopsy.

FUNDING INFORMATION

Target RWE is the sponsor of the TARGET-NASH study.

CONFLICTS OF INTEREST

Heather L. Morris, Feng Yu, Andrea R. Mospan: employees of Target RWE. Miriam B. Vos: consultant to Target RWE, Eli Lilly, Boehringer Ingelheim, Madrigal, and Inventiva. Advisor to Albireo. Grants from Target RWS, Labcorp and Sonic Incytes. Stock in Thiogenesis and Tern. Anna Mae Diehl: Grants from Boehringer Ingelheim, Tune Therapeutics, Hepta-Bio, Intercept, Hanmi, Viking, and GlaxoSmithKline. Daniel H. Leung: Advisor to AstraZeneca and Vertex. Grants from Gilead and Cystic Fibrosis Foundation. James E. Squires: advisor to Sanofi. The remaining authors have no conflicts to report.

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