INASL–SAASL Consensus Statements on NAFLD Name Change to MAFLD

Shivaram P. Singh [*,#], Ajay Duseja [†,#], Mamun al Mahtab [‡], Prajna Anirvan [*], Subrat K. Acharya [§], Sheikh Mohammad Fazle Akbar [‖], Amna S. Butt [¶], Anuradha Dassanayake [#], Arka De [†], G. P. Dhakal [**], Saeed Hamid [††], Kaushal Madan [‡‡], Manas K. Panigrahi [§§], P. N. Rao [‖‖], Sanjiv Saigal [¶¶], Sanjaya K. Satapathy [##], Shalimar [***], Ananta Shrestha [†††], Akash Shukla [‡‡‡], K. C. Sudhamshu [§§§], Hasitha Wijewantha [‖‖‖]

[*]*Kalinga Gastroenterology Foundation, Cuttack 753001, Odisha, India,* [†]*Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India,* [‡]*Department of Interventional Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh,* [§]*Department of Gastroenterology and Hepatology, KIIT University, Patia, Bhubaneshwar 751024, Odisha, India,* [‖]*Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Toon, Ehime, Japan,* [¶]*Section of Gastroenterology, Department of Medicine, The Aga Khan University Hospital, Karachi, Sindh, Pakistan,* [#]*Colombo North Centre for Liver Disease, Faculty of Medicine/University of Kelaniya, Colombo, Sri Lanka,* [**]*Jigme Dorji Wangchuck National Referral Hospital (JDWNRH), Khesar Gyalpo University of Medical Sciences of Bhutan (KGUMSB), Thimphu, Bhutan,* [††]*Department of Medicine, Aga Khan University, Karachi, Pakistan,* [‡‡]*Department of Gastroenterology and Hepatology, Max Smart Super Specialty Hospital, Saket, New Delhi, 110017, India,* [§§]*Department of Gastroenterology, All India Institute of Medical Sciences, Bhubaneswar, 751019, India,* [‖‖]*Department of Hepatology, Asian Institute of Gastroenterology, Hyderabad, 500082, India,* [¶¶]*Department of Hepatology, Medanta Hospital, Gurugram, 122001, India,* [##]*Sandra Atlas Bass Center for Liver Diseases & Transplantation, Department of Medicine, North Shore University Hospital/Northwell Health, 400 Community Drive, Manhasset, NY 11030, USA,* [***]*Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, 110016, India,* [†††]*Liver Foundation Nepal, Kathmandu, 44600, Nepal,* [‡‡‡]*Department of Gastroenterology, Seth GSMC & KEM Hospital, Mumbai, 400022, India,* [§§§]*Liver Unit, Department of Medicine, Bir Hospital, Kathmandu, Nepal and* [‖‖‖]*Department of Gastroenterology and Hepatology, Provincial General Hospital, Badulla, Sri Lanka*

There is an ongoing debate on the change of terminology of non-alcoholic fatty liver disease (NAFLD) to metabolic associated fatty liver disease (MAFLD). Experts from the Indian National Association for Study of the Liver (INASL) and the South Asian Association for Study of the Liver (SAASL) involved in diagnosing, managing, and preventing NAFLD met in March 2022 to deliberate if the name change from NAFLD to MAFLD is appropriate, as proposed by a group of experts who published a "consensus" statement in 2020. Proponents of name change to MAFLD opined that NAFLD does not reflect current knowledge, and the term MAFLD was suggested as a more appropriate overarching term. However, this "consensus" group which proposed the name change to MAFLD did not represent the views and opinions of gastroenterologists and hepatologists, as well as perceptions of patients across the globe, given the fact that change of nomenclature for any disease entity is bound to have multidimensional impact on all aspects of patient care. This statement is the culmination of the participants' combined efforts who presented recommendations on specific issues concerning the proposed name change. The recommendations were then circulated to all the core group members and updated based on a systematic literature search. Finally, all the members voted on them using the nominal voting technique as per the standard guidelines. The quality of evidence was adapted from the Grades of Recommendation, Assessment, Development and Evaluation system. (J Clin Exp Hepatol xxxx;xxx:xxx)

In 2020, a group of experts published a "consensus" statement advocating the need for a change in the terminology of non-alcoholic fatty liver disease (NAFLD) to metabolic-associated fatty liver disease (MAFLD).[1] According to this group of experts, a name change was necessary because apparently, the current term "NAFLD" does not accurately represent the pathophysiology of the disease, is heterogenous and represents a disease of exclusion besides being stigmatising to the patients. The Indian National Association for Study of the Liver (INASL) and the South Asian Association for Study of the Liver (SAASL) which represent the gastroenterologists and hepatologists involved in the diagnosis, management and prevention of NAFLD in India and South Asia felt the need for a consensus statement given the fact that while India and South Asia harbor the largest chunk of NAFLD patients worldwide. The unique perceptions among South Asian NAFLD patients regarding various aspects of the disease differ considerably from other parts of the world. Therefore, any change to an existing terminology should reflect advancements in our understanding of the disease, and should also be inclusive and respect patients' sentiments, beliefs, and attitudes.

Keywords:: fatty liver, terminology, name change, stigma, South Asia
Received: 15.11.2022; *Accepted:* 19.12.2022; *Available online:* xxx
Address for correspondence.
E-mails: fattyliver@gmail.com or ajayduseja@yahoo.co.in
[#]Both Shivaram Prasad Singh and Ajay Duseja contributed equally to this manuscript.
https://doi.org/10.1016/j.jceh.2022.12.011

Please cite this article as: Singh et al., INASL–SAASL Consensus Statements on NAFLD Name Change to MAFLD, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.12.011

METHODS

The INASL-SAASL consensus group included experts with experience/publications in NAFLD management from different parts of India and South Asia. They were invited to participate in the consensus development process on the name change of NAFLD to MAFLD to establish an updated document on the nomenclature of NAFLD. The consensus group was divided into two teams to study six major questions concerning the proposed name change and synthesize statements for consensus development. The teams reviewed the following aspects: Team 1—should NAFLD be changed to MAFLD? Why should NAFLD not be changed to MAFLD? What are the demerits of name change to MAFLD? Team 2—will a name change make the disease more homogeneous? Does the term NAFLD stigmatize the NAFLD patients? Does "non" in the term "NAFLD" trivialize the disease?

Experts reviewed all pertinent literature on the subject with special reference to the Indian and South Asian data. After thorough brainstorming, appropriate statements on various aspects were prepared and subjected to voting among the entire group. This consensus was produced through a modified Delphi process involving multiple rounds of virtual meetings. All statements prepared were submitted for the final consensus voting during a combined meeting. Eighty percent or higher votes were considered acceptable for the final statement. Based on the available evidence, the statements were reviewed and voted for any of the five options. The options given for each statement were (a) accept completely, (b) accept with some reservation, (c) accept with major reservation, (d) reject with reservation, and (e) reject completely. Consensus on a statement was achieved when 80% or more of the voting members chose to "accept completely" or "accept with some reservation" in favor of the statement. The statements were "rejected" if 80% of voting members voted for either reject with reservation or reject completely. Statements that were not found acceptable were modified for a final round of voting if the voting members felt so. The revised statements were again subjected to voting for either acceptance or rejection. Subsequently, the relevant data were presented, and the level of evidence and strength of recommendation were graded using a modified protocol proposed by the Canadian Task Force on the Periodic Health Examination (Table 1).[2] The group of experts achieved a consensus on the following 6 statements on the issue of name change from NAFLD to MAFLD.

Need for change in terminology

Statement 1: The term NAFLD [non-alcoholic fatty liver disease] should not be changed to MAFLD

Level of evidence: II-3
Grade of recommendation: A
Agreement: 100%

The generic archetypal acronym NAFLD appears perfect for a heterogeneous condition which involving numerous disruptions in multiple pathways that are often overlapping, but occasionally exclusive, and stands out phenotypically by the singular denominator that is hepatic steatosis, exclusively in individuals who consume little or no alcohol. In medical science, nomenclatures evolve, and names change to accommodate new knowledge that brings a paradigm shift in our understanding of a disease, including its management and outcomes. Ever since the days when NAFLD was first described, there has been a steady and progressive refinement in our understanding of the pathophysiological aspects and management approach of the entity. Over the years, the heterogeneity and multifactorial pathogenesis of NAFLD has become apparent, evolving from a single hit through two-hit to multiple hits pathway. The current attempt at forcefully homogenizing NAFLD with this terminological intervention reverses everything that has been discovered, and undo all the new knowledge acquired about the pathogenesis over the past few decades. Therefore, any change in the terminology would be appropriate only in the context of a novel, ground breaking research that completely alters our current understanding of the disease or adds a whole new dimension to it. The inappropriateness of the term "'MAFLD" lies in the fact that it tries to unsuccessfully

Table 1 Grading of Recommendations: Quality of Evidence and Strength of Recommendation.

Level of Evidence		Strength of recommendation	
Grade	Description	Grade	Description
I	Evidence obtained from at least one randomized controlled trial	A	There is good evidence to support the statement
II-1	Evidence from well-controlled trials without randomization	B	There is fair evidence to support the statement
II-2	Evidence from well-designed cohort or case–control study	C	There is poor evidence to support the statement
II-3	Evidence from comparison between time or place with or without intervention	D	There is fair evidence to refute the statement
III	Opinion of experienced authorities or expert committees	E	There is good evidence to refute the statement

Modified from the 1984 updated proposal of the Canadian Task Force on the Periodic Health Examination.

Please cite this article as: Singh et al., INASL–SAASL Consensus Statements on NAFLD Name Change to MAFLD, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.12.011

homogenise a vastly heterogeneous entity like NAFLD into a solely metabolically driven disease, to which paradoxically so many other liver diseases can be clubbed together including alcohol-associated liver disease which is also metabolically driven.[3] This attempt to change the terminology without a compelling and genuine reason is confusing. There could be multiple reasons for direct and deliberate changes in science and medicine. At the same time, there could also be genuine reasons for opposing the changes, leading to the rejection of the nomenclature revision. Of late, there has been a debate regarding the change in terminology of certain aspects of human anatomy. For example, the term "arteria" which is derived from Greek "αήρ" and "τηρώ" (aérteró) meaning "'air" and "'hold" could be changed to "hemteria" meaning "blood" and "hold" based on its function.[4] However, this could potentially disrupt human as well as veterinary science and even public life, and therefore, is likely to be rejected worldwide. Thus, it is evident that the reasons put forth to justify the name change do not provide valid arguments for changing the terminology.[4]

Reasons for a name change

Statement 2: The reasons for not changing are many, but the most important one is that there are no cogent reasons to justify a name change

Level of evidence: II-2
Grade of recommendation: B
Agreement: 100%

MAFLD is an acronym for "metabolic-associated fatty liver disease." There is an inherent flaw in grammar in this term. The word "metabolic" itself connotes something that is "metabolism associated!" Hence, it is inappropriate to use "associated" again after metabolic. In addition, there is much more to NAFLD than the mere presence of dysmetabolism. It has been observed in several studies, especially from South Asia, that a significant proportion of our NAFLD patients don't have insulin resistance, and insulin resistance is not the sole factor driving disease in NAFLD. Two studies—one from India and the other from Bangladesh—showed that 50%–60% of NAFLD patients in this region did not have insulin resistance.[5,6] In addition, there is enough evidence to show that genetic polymorphism, bile acid fluctuations, gut dysbiosis and environmental stressors drive disease progression in NAFLD independent of BMI and insulin resistance.[7–10] It is also very clear that the pathogenesis of NAFLD involves multiple players and cannot solely be ascribed to metabolic dysfunction alone. The occurrence of "NAFLD" in lean individuals in whom factors like gut dysbiosis and bile acid fluctuations play significant roles also lend credence to this observation.[11] While defining MAFLD, it was stated that "a reference to alcohol should not be included in the MAFLD acronym" and that "MAFLD can co-exist with other liver diseases." [1] This definition of MAFLD is self-contradictory because while on one hand, the proponents of MAFLD have highlighted the heterogeneity in NAFLD as one of the major reasons that have necessitated this name change, this definition of MAFLD, which allows for significant consumption of alcohol has made the entity even more heterogeneous. Thus, it is obvious there are no valid reasons to justify this change in nomenclature.

Demerits of the proposed name change

Statement 3: A name change from NAFLD to MAFLD is replete with demerits

Level of evidence: II-3
Grade of recommendation: B
Agreement: 100%

A major fall out of name change is possibly the '"re-branding" going wrong. The use of the term "brand" may seem inappropriate in the setting of medical academia, but changes in medical terminology are not all about academics. It has taken almost half a century of persistent advocacy efforts, and that non-hepatologists are beginning to recognize the importance of "NAFLD"; changing this name to another without robust evidence, either pathogenetic or perceptive, can have serious consequences. In this context, it is pertinent to note that soon after the publication of this "consensus" statement on MAFLD, several leading NAFLD experts from the original 'international panel' defected and soon came out with a commentary emphatically cautioning against the grave implications of a premature change in terminology.[12] The unsustainable change of nomenclature has also been opposed because NAFLD is treated not only by hepatologists, but also by cardiologists, diabetologists and primary care providers.[13] It has taken such a long time to develop, consolidate and disseminate the knowledge acquired about NAFLD and its pathophysiological aspects and, at the same time, devise therapeutics to counter this growing pandemic. In this regard, it is worth mentioning that recently, India took the lead and became the first and only country in the world to lead the fight against the NAFLD pandemic by launching a program to integrate NAFLD into its National Programme for Prevention and Control of Cancer, Diabetes, CVD and Stroke. Therefore, a name change could create unnecessary clinical confusion and coding issues. At the same time, disease awareness, research development, drug development and biomarker development may be affected by this change, leading to a significant setback in NAFLD research. By targeting metabolic syndrome alone, this rebranding might paradoxically misdirect therapeutics in the long run. The name change will create confusion among non-hepatologists, funding agencies, regulatory agencies, policy makers.

Please cite this article as: Singh et al., INASL–SAASL Consensus Statements on NAFLD Name Change to MAFLD, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.12.011

Issue of heterogeneity

Statement 4: A name change will make the disease even more heterogeneous

Level of evidence: II-2
Grade of recommendation: A
Agreement: 100%

The proponents of MAFLD themselves acknowledge that multiple players are involved in the pathogenesis of NAFLD. The heterogeneity in MAFLD, as per the "consensus" group, is due to "different disease subtypes, variable natural history, inter-individual variation, and variable response to therapy." In addition, all individuals who have NAFLD don't have metabolic syndrome or other metabolic risk factors. In a recent comparative study of MAFLD and NAFLD diagnostic criteria in the real world, out of a total of 13 083 from the NHANES III database, MAFLD was diagnosed in 4087/13 083 (31.24%) participants, while NAFLD was diagnosed in 4347/13 083 (33.23%) amongst the overall population and 4347/12 045 (36.09%) in patients without alcohol intake and other liver diseases.[14] Furthermore, it needs to be reiterated that insulin resistance and hepatic steatosis share a complex bi-directional relationship.[15] NAFLD can even precede metabolic dysfunction. The MAFLD proponents have not considered this important pathophysiological aspect. Besides, the applicability of the MAFLD criteria in a real-life setting in India has also been examined.[16] In a retrospective analysis of 1040 patients with NAFLD-managed prospectively in a real-life setting over 10 years, by applying MAFLD criteria, 88% patients qualified as having MAFLD. Among the remaining 124 (12%) non-diabetic, lean patients applying the criteria for metabolic-dysfunction as per the MAFLD "consensus" statement, 38.7% patients were labeled as lean MAFLD. The remaining 61.3% remained as non-MAFLD-lean NAFLD patients, thereby highlighting the poor applicability of these criteria in real life in a significant proportion of patients.

Patients' perceptions and stigmatization

Statement 5: The term "NAFLD" does not stigmatize patients. Instead, patients are happy being labeled as "non-alcoholic"

Level of evidence: II-2
Grade of recommendation: A
Agreement: 100%

The claim by the "consensus" group that the term NAFLD is stigmatizing to patients is contentious. In a survey conducted on 218 patients across multiple countries in South Asia, it was observed that an overwhelming majority of the patients did not find the term "NAFLD" disrespectful.[17] Importantly, once patients were labeled "NAFLD," they were not subjected to repeated grilling by physicians regarding alcohol intake; this is of particular significance because alcohol is considered taboo in South Asian societies and asking a patient about alcohol intake is humiliating to patients and is considered improper. These unique socio-cultural aspects are not prevalent in Western countries. Therefore, it is clear that the proponents of MAFLD have overlooked these cultural variations in patient perceptions across societies. This observation in South Asian NAFLD patients refutes their claim that the term "NAFLD" is stigmatizing to patients. Another aspect that is of concern is the application of MAFLD criteria to the pediatric population. Metabolic liver diseases in children are entirely different, and labeling children "MAFLD" would create more confusion.

The use of the word "non" and trivialization of the disease

Statement 6: The term "non" in non-alcoholic fatty liver disease does not trivialize the disease

Level of evidence: II-2
Grade of recommendation: A
Agreement: 100%

The claim that the use of the word "non" in Non-alcoholic Fatty Liver Disease trivializes the disease is also not supported by evidence. In the study which was conducted amongst South Asian patients, it was observed that South Asian patients strongly felt that the use of the word "non" did not in any way trivialize their problem.[17] On the contrary, it protected them from repeated humiliating questioning about alcohol intake. 86.3% of patients found the term "NAFLD" consoling and 83% did not feel that "non" in NAFLD trivialized their problem. In Medicine, numerous examples have used a negative definition to describe a disease entity. The World Health Organization defines "health" as an absence of disease. Other conditions include non-Hodgkin lymphoma, non-communicable diseases and non-small-cell lung cancer. Further, non-Hodgkin lymphoma encompasses a diverse variety of lymphomas with different tumour behaviour and thus is a heterogeneous entity; however, the terminology does not trivialize the disease.

The attempt to change the terminology from "NAFLD" to "MAFLD" is confusing and is not evidence-based. Since NAFLD is not merely the hepatic "manifestation" of metabolic syndrome, it would be erroneous to term it "MAFLD." Including significant amounts of alcohol intake in the MAFLD criteria makes it even more confusing and would cause problems in the real-world setting since non-hepatologists evaluate a huge number of NAFLD patients. Patients' perceptions regarding disease vary worldwide. A change in terminology should be "inclusive," respecting the sensitivities of all patient populations and be "realistic."

Please cite this article as: Singh et al., INASL–SAASL Consensus Statements on NAFLD Name Change to MAFLD, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.12.011

EPILOGUE

Using the oft quoted Shakespearean theme of the red rose and its scent, it can be emphasised that it is not the name but the disease that decides the outcome of patients with fatty liver disease. A hasty change of name, without taking into account the complex peculiarities and the variations across populations, is fraught with disastrous consequences. Perhaps we could take a cue from the St. Petersburg-Leningrad saga and realise the futile waste of time and resources such decisions could result in. We could also do well to shun our ego, keep aside our pedagogy and focus on curbing the spiralling menace of NAFLD. Perhaps this is what one modern writer meant when she said, "never argue with a pedant over nomenclature. It wastes your time and annoys the pedant!"

CONFLICTS OF INTEREST

All authors have none to declare.

SOURCE OF FUNDING

The preparation of the consensus statements was partially supported by a grant from the Kalinga Gastroenterology Foundation, Cuttack, Odisha.

REFERENCES

1. Eslam M, Sanyal AJ, George J. International consensus panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*. 2020;158:1999–2014.e1. https://doi.org/10.1053/j.gastro.2019.11.312.
2. The periodic health examination: 2. 1984 update. Canadian Task Force on the periodic health examination. *Can Med Assoc J*. 1984;130:1278–1285.
3. Duseja A, Taneja S. Changing nomenclature from nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease – not only premature but also confusing. *J Clin Exp Hepatol*. 2021;11:278–279. https://doi.org/10.1016/j.jceh.2020.08.002.
4. Kachlik D. Changes of anatomical nomenclature must be deliberate: the female external genitalia. *Clin Anat*. 2021;34:320–323. https://doi.org/10.1002/ca.23672.
5. Singh SP, Misra B, Kar SK, et al. Nonalcoholic fatty liver disease (NAFLD) without insulin resistance: is it different? *Clin Res Hepatol Gastroenterol*. 2015;39:482–488. https://doi.org/10.1016/j.clinre.2014.08.014.
6. Azam G, Alam S, Hasan SN, Alam SMNE, Kabir J, Alam AK. Insulin resistance in nonalcoholic fatty liver disease: experience from Bangladesh. *Bangladesh Crit Care J*. 2016;4:86–91. https://doi.org/10.3329/bccj.v4i2.30022.
7. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet*. 2008;40:1461–1465. https://doi.org/10.1038/ng.257.
8. Caussy C, Hsu C, Singh S, et al. Serum bile acid patterns are associated with the presence of NAFLD in twins, and dose-dependent changes with increase in fibrosis stage in patients with biopsy-proven NAFLD. *Aliment Pharmacol Ther*. 2019;49:183–193. https://doi.org/10.1111/apt.15035.
9. Da Silva HE, Teterina A, Comelli EM, et al. Nonalcoholic fatty liver disease is associated with dysbiosis independent of body mass index and insulin resistance. *Sci Rep*. 2018;8:1466. https://doi.org/10.1038/s41598-018-19753-9, 23.
10. Abid A, Taha O, Nseir W, Farah R, Grosovski M, Assy N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. *J Hepatol*. 2009;51:918–924. https://doi.org/10.1016/j.jhep.2009.05.033.
11. Chen F, Esmaili S, Rogers GB, et al. Lean NAFLD: a distinct entity shaped by differential metabolic adaptation. *Hepatology*. 2020;71:1213–1227. https://doi.org/10.1002/hep.30908.
12. Younossi ZM, Rinella ME, Sanyal AJ, et al. From NAFLD to MAFLD: implications of a premature change in terminology. *Hepatology*. 2021;73:1194–1198. https://doi.org/10.1002/hep.31420.
13. Hashimoto E, Tokushige K, Ludwig J. Diagnosis and classification of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: current concepts and remaining challenges. *Hepatol Res*. 2015;45:20–28. https://doi.org/10.1111/hepr.12333.
14. Kim D, Konyn P, Sandhu KK, Dennis BB, Cheung AC, Ahmed A. Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. *J Hepatol*. 2021;75:1284–1291. https://doi.org/10.1016/j.jhep.2021.07.035.
15. den Boer M, Voshol PJ, Kuipers F, Havekes LM, Romijn JA. Hepatic steatosis: a mediator of the metabolic syndrome. Lessons from animal models. *Arterioscler Thromb Vasc Biol*. 2004;24:644–649. https://doi.org/10.1161/01.ATV.0000116217.57583.6e.
16. De A, Ahmad N, Mehta M, Singh P, Duseja A. NAFLD vs. MAFLD – it is not the name but the disease that decides the outcome in fatty liver. *J Hepatol*. 2022;76:475–477. https://doi.org/10.1016/j.jhep.2021.09.002.
17. Singh SP, Anirvan P, Butt AS, et al. NAFLD vs MAFLD: South Asian NAFLD patients don't favor name change. *Euroasian J Hepato-Gastroenterol*. 2022 Jul;12(suppl 1):S1–S4. https://doi.org/10.5005/jp-journals-10018-1363.

Please cite this article as: Singh et al., INASL–SAASL Consensus Statements on NAFLD Name Change to MAFLD, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.12.011