

Recent International Consensus-Based Changes in the Diagnostic Criteria and Nomenclature of Nonalcoholic Fatty Liver Disease

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Accumulation of fat in the liver, popularly called fatty liver disease (FLD), is a highly prevalent pathological condition. It is characterised by the accumulation of variable amounts of triglycerides in the hepatocytes which may or may not be associated with liver injury. FLD has many causes and equally heterogeneous pathogenetic mechanisms, clinical courses, and outcomes. Conventionally, FLD was segregated into two main categories: Alcohol-associated liver disease (ALD) and Nonalcoholic FLD (NAFLD). Proper terminology and classification of the latter have been problematic since its initial recognition in the 1980s when Ludwig *et al.* described detailed pathological features of the condition in a cohort of 20 patients with no history of alcohol abuse and christened the disease as nonalcoholic steatohepatitis (NASH).¹ The broader term NAFLD was first used in a review article by Schaffner and Thaler in 1986.²

Since these earlier portrayals of NAFLD, substantial progress has been made in understanding the disease's epidemiology, aetiology, pathogenesis, pathology, treatment, and prognosis.³⁻⁶ In particular, the prevalence of the disease has risen sharply throughout the world, and it has attained epidemic proportions affecting more than 40% of the world's adult population in most recent surveys. It has become the foremost cause of chronic liver disease (CLD) and the dominant indication of liver transplantation globally.^{7,8} Of particular concern is the fact that its incidence and prevalence have also increased significantly in children with the rise in the rates of childhood obesity. The disease is also reported commonly in non-obese individuals (lean NAFLD). The rise in prevalence in adults is particularly linked to the rise in the incidence of obesity, Type 2 Diabetes (T2D), and metabolic syndrome (MS).³⁻⁵ An association of the disease with cardiovascular risks has also been reported in many studies, thus further complicating the disease's aetiology and pathogenesis.^{3,4}

Although there is no specific treatment for the disease to date, considerable progress has been made in understanding the pathogenesis and molecular mechanisms of the disease. These advancements have made it possible to develop novel biomarkers for non-invasive diagnosis and monitoring of disease and targeted therapies, paving the way for personalised care in the near future. This vast expansion of knowledge and progression in understanding the disease were not reflected neither in the nomenclature of the disease nor its diagnostic criteria until very recently. All the above developments necessitated a revisiting of the terminology, diagnostic criteria, and classification of the disease.⁹ Numerous attempts were made to address these issues but none achieved widespread global acceptance. The two main objections to the use of the term NAFLD have been that it was based on negative or exclusionary diagnostic criteria, and there were two stigmatising terms in the name, i.e., alcohol and fatty.⁹ Moreover, there was no linkage to the main underlying aetiology or risk factors of the disease in the name. Besides, the previous nomenclature excluded patients with predisposing conditions for NAFLD, such as T2D, who consumed greater quantities of alcohol than the stringent criteria for nonalcoholic thresholds.

In 2020, a group of international liver experts proposed metabolic dysfunction-associated FLD (MAFLD) as a substitute for the term NAFLD, to highlight the cardinal role of systemic metabolic derangements in the etiopathogenesis of this disease.^{9,10} They suggested MAFLD as the single all-embracing term for the entire spectrum of NAFLD (Figure 1). They also proposed positive diagnostic criteria for a positive diagnosis of MAFLD. The change of the terminology was done with the goal of highlighting the crucial role of metabolic factors in the causation and pathogenesis of the disease, thus improving patient understanding of the disease, facilitating patient-physician communication, and emphasising the importance of public health interventions in its prevention and management. However, the new term still included stigmatising terms and did not cover the entire range of steatotic liver disease (SLD). Thus, the heterogeneous characteristic of NAFLD was ignored in MAFLD. Moreover, not all cases of NAFLD are seen in obese or fatty individuals. These can be seen in lean individuals. They also removed the term, steatohepatitis, a key lesion in progressive forms of FLD, from the new arrangement. Several associations specialising in the study of liver diseases ratified the new name. However, a broader international acceptance was not

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achieved, and a substantial number of important pan-national and national societies did not fully endorse the new terminology. Many liver experts described it as a premature and incomplete attempt. Concerns were also raised on the robustness and transparency of the methodology used for changing the name.

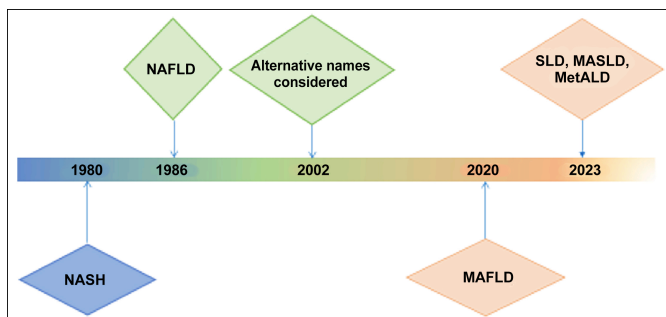


Figure 1: Schematic diagram showing the main developments in the evolution of terminology of fatty liver diseases (FLD), particularly, non-alcoholic FLD (NAFLD). The most recent name suggested was the umbrella term of steatotic liver disease (SLD). NASH, Nonalcoholic steatohepatitis; MAFLD, Metabolic dysfunction-associated fatty liver disease; MASLD, Metabolic dysfunction-associated SLD; MetALD, MASLD in combination with moderate alcohol consumption.

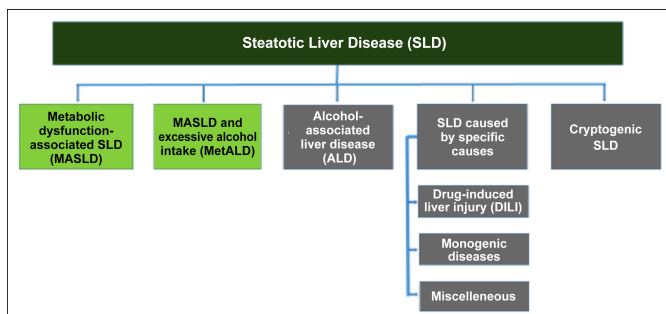


Figure 2: Steatotic Liver Disease (SLD) and its classification. This figure displays the plan for SLD and its sub-division into five categories. SLD, diagnosed on imaging studies or biopsy, has many possible causes. MASLD, characterised by hepatic steatosis along with one cardio-metabolic risk factor (CMRF) and no other recognisable cause, ALD, and a mixture of the two (MetALD), constitute the most prevalent causes of SLD in a clinical practice. Other specific aetiologies of SLD need to be categorised separately, as they demonstrate distinctive pathogenesis. Multiple causes of steatosis can occur together in one case. Individuals with no discernable cause are presently placed under the cryptogenic SLD category. However, these may be reclassified in the future in response to an increase in the understanding of disease pathophysiology.

In view of the above deficiencies and objections, a renewed global effort was initiated in 2020 under the auspices of three pan-national liver associations namely the American Association for the Study of Liver Diseases (AASLD), the *Asociación Latinoamericana para el Estudio del Hígado* (ALEH), and the European Association for the Study of the Liver (EASL) for a more representative name and diagnostic parameters for the disease. The new nomenclature was developed from 2020 to early 2023 and was finally announced in June 2023. The global consultation process used the structured, transparent, multi-stage survey-based Delphi technique along with hybrid meetings. In the process, around 236 experts from 56 countries, and members of the NAFLD Nomenclature Consensus Group,

contributed to a total of four online surveys along with two in-person meetings. A final response rate of >75% was achieved for four rounds of data gathering. Since the term 'nonalcoholic' was previously renamed, the term 'fatty' was swapped with steatosis, a scientific and non-stigmatising term. SLD was chosen as an all-encompassing term to embrace all possible aetiologies of steatosis including ALD (Figure 2). A total of five diagnostic sub-categories were generated to encompass the entire spectrum of FLDs including ALD and combined forms of the disease. The term steatohepatitis was retained as it was considered to be a crucial pathophysiological step and an integral part of the natural course and evolution of the disease. The term metabolic dysfunction-associated SLD (MASLD) was selected as a substitute for NAFLD. An agreement was also reached on changing the diagnostic criteria to include at least one of the cardiometabolic risk factors (CMRFs). These are different for adult and paediatric patients. Metabolic dysfunction-associated steatohepatitis (MASH) was chosen to replace the term NASH. The cryptogenic SLD category was reserved for those patients who had no metabolic risk factors or no known causes (Figure 2). Because of the common coincidence of the two conditions, a new sub-category of MetALD was created to describe individuals with MASLD who drink above-threshold quantities of alcohol per week. The Delphi panel devised an algorithmic approach for categorising the disease in individual patients which will be very helpful in a clinical practice. According to proponents of the new nomenclature, this metamorphosis will serve to increase disease awareness among patients and clinicians, eradicate stigma, and speed up the development of biomarkers and drugs to benefit patients with MASLD and MetALD.¹¹ It should be noted that the name change does not alter the natural history, biomarkers, or trials. The staging and grading of the disease will also not be affected by this change of terminology. The Delphi group demarcated and defined a sub-category, MetALD, that has received very little attention till now, which will get due attention, and will get integrated into care pathways and included in clinical trials.

In conclusion, the new terminology, categorisation, and defining criteria for FLD are broadly supported, non-stigmatising, and provide a new and powerful platform for the medical community to intensify disease awareness, abolish stigma, and speed up biomarker and targeted treatment development for improved management of patients afflicted with various conditions within the umbrella of SLD spectrum.

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