Article category: Editorial

Title
From NASH, MAFLD, to SLD: updates of nomenclature and impact on clinical trials

Author
Ming-Lun Yeh¹,², Ming-Lung Yu¹,²,³

Affiliations
¹School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.
²Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.
³School of Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung, Taiwan.

Correspondence: Ming-Lung Yu, M.D., Ph.D.
Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Tzyou Road, Kaohsiung City 807, Taiwan.
Financial Support: None

Conflict of interest: All authors have no conflict of interest related to this publication.

Word counts: 1393, reference: 20

Keywords: NAFLD, MAFLD, SLD, MASLD, Steatosis

Authors’ contribution: ML Yeh drafted the manuscript. ML Yu reviewed and finalized the manuscript.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, Metabolic Dysfunction
Associated Steatotic Liver Disease; HBV, hepatitis B virus; HCV, hepatitis C virus; SLD, Steatotic Liver Disease; CMRFs, cardiometabolic risk factors; ALD, Alcohol-related liver disease; MASH, metabolic associated steatohepatitis; HDL, high density lipoprotein; SGLT2, glucose-lowering agents, sodium-glucose cotransporter 2; GLP1, glucagon-like peptide 1.
With the growing prevalence, nonalcoholic fatty liver disease (NAFLD) has become the primary etiology of liver disease globally.\textsuperscript{1,2} However, the exclusionary diagnostic criteria raise concerns about using the term "NAFLD". In 2020, a panel of international experts from 22 countries proposed a new nomenclature of "metabolic dysfunction-associated fatty liver disease (MAFLD)" by a panel of experts in this field.\textsuperscript{3} As the name suggests, MAFLD emphasizes the importance of metabolic dysfunction that can be observed from the new definitions of overweight/obesity, type 2 diabetes, or at least two metabolic risk abnormalities, irrespective the etiologies and comorbidities, such as alcoholism and viral hepatitis. However, ignoring alcoholism and other specific etiologies raise concern about the contributions of hepatic steatosis in the progression of liver disease and the stigmatization of the term "fatty". Recently, a new nomenclature, "Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)" was set up by three pan-national liver associations to replace “NAFLD” and “MAFLD”.\textsuperscript{4,5}

In the current \textit{Clinical and Molecular Hepatology} issue, Kim et al.\textsuperscript{6} presented their views regarding the potential impact of the new nomenclature “MASLD” on screening, diagnosis, treatment, and future drug development. Perspectives from hepatologists and endocrinologists were included, too. Unlike the negative criterion of
NAFLD, MAFLD used a positive criterion and focused more on the linkage of metabolic abnormalities that were seen by the diagnostic criteria. More patients are diagnosed without the exclusion of other specific etiologies, and the disease awareness of physicians and patients is also improved. The most common cause of mortality in NAFLD patients was cardiovascular disease, followed by extrahepatic cancers.\textsuperscript{7} It had been reported that MAFLD patients had a greater risk for all-cause mortality than NAFLD patients.\textsuperscript{8} Other reports also demonstrated an increased cardiovascular mortality of patients with MAFLD as compared to NAFLD.\textsuperscript{9} Similar results were also found in the risk of all types of cancers.\textsuperscript{10} That means the transition from NAFLD to MAFLD helps identify more subjects who are at risk of extrahepatic events, and further promotes the surveillance of extrahepatic diseases in clinical practice. Moreover, MAFLD also provide the chance to evaluate the interaction between NAFLD and hepatitis B virus (HBV) and hepatitis C virus (HCV).\textsuperscript{11}

However as mentioned in this review, the abandonment of “steatohepatitis” disturbs the evaluation of hepatic severity and development of pharmaceutical agents. Meanwhile, the total ignoring of alcohol consumption in MAFLD may confuse the clinical judgment regarding the contributions of alcohol in hepatic progression. It is the same with the other specific etiologies that will also lead to hepatic steatosis and disease progression.
Different from NAFLD and MAFLD, the new term "Steatotic Liver Disease (SLD)" separates patients with or without cardiometabolic risk factors (CMRFs) and further classifies patients with CMRFs as “MASLD” which indicates no specific etiology of steatosis, and “MetALD or other combined etiology” for those with a moderate amount of alcohol consumption or drug, monogenic disease related steatosis. Those without CMRFs are categorized as “Alcohol-related liver disease (ALD)”; or "Specific etiology SLD” like drug-induced, monogenic, and miscellaneous, and "Cryptogenic SLD" than not belong to the above categories. The new “MASLD” also considers the hepatic progression form with a new term, "metabolic associated steatohepatitis (MASH)" which can be used as future guidance in clinical trials. The definition of alcohol amount is one of the points that SLD is different from NAFLD and MAFLD. Unlike the strict threshold of alcohol amounts in NAFLD and no threshold in MAFLD. A new category, "MetALD” is set up for those who consume moderate amounts of alcohol. The alcohol criteria of MetALD were made by general agreement that 30-60 gm of daily alcohol consumption would affect the natural history of NAFLD and possibly alter the response to therapeutic interventions. Recently, data from UK Biobank demonstrated that the MetALD group comprises predominantly males, and diabetes mellitus was significantly more prevalent in the MASLD group. The MetALD group also exhibits higher levels of
liver enzymes but lower levels of high density lipoprotein (HDL) cholesterol. The data implied the potential role of dyslipidemia in the pathogenesis and differentiation of MetALD and MASLD.

From the perspectives of hepatologists, both of the two new terminologies can increase disease awareness among patients and physicians. It is also expected to affect clinical practice positively, like the diagnostic process, non-pharmacologic approach and potential treatment candidates. For clinical outcomes, the new subtypes of SLD might help identify more subjects at risk, either hepatic or extrahepatic. Different alcohol amounts separate subjects with alcohol consumption in the new terminology that enables the development of proper treatment strategies accordingly and further helps to understand the influences of alcohol consumption in disease progression. Nevertheless, the criteria of alcohol consumption remain based on experts’ opinion and agreement, without scientific evidence. It is also difficult to assess alcohol consumption precisely in clinical practice.

The FDA recommends endpoints of clinical trials for accelerated approval for NASH, including either improvement in steatohepatitis or fibrosis. Thus, MAFLD is usually not included in the clinical trial enrollment criteria because of the lack of the term “steatohepatitis”. The new MASLD, with the progression form MASH, is expected to allow clinical trial enrollments. However, MASH also exclude NASH
patients without CMRFs from NASH treatment, even it might be rare. Whether the potential therapeutic agents for NASH could be generalized to MASH patients needs further investigation.

Although that, several challenging issues of SLD are concerned.

1) There is difficulty in developing disease-specific biomarkers or agents for patients of MASLD, MetALD and ALD. The dynamic changes in metabolic health and alcohol consumption over time also raised the concern of making the diagnosis at a specific time. Currently, subjects who consume a high amount of alcohol together with metabolic dysfunction (positive CMRFs) are classified as ALD. However, this group of patients may have different disease pathogenesis, course and outcomes to those without metabolic dysfunction.

2) Patients with HCV infection are classified as "Miscellaneous SLD". At least 20% of subjects have a spontaneous resolution from acute HCV infection, and most of the chronically infected patients are now eradicated owing to the current high-efficacy antiviral drugs. Chronic HCV infections are associated with risks of extrahepatic manifestations which frequently correlates to fatty liver, DM, cardiovascular comorbidities, even after HCV eradication. The role of metabolic dysfunction in the development of SLD before and after HCV eradication is clinically importance, which should not be excluded from clinical practice for SLD. Whether classifying it
as HCV-SLD or HCV-MASLD may need further exploration.

3) HBV infection remained highly prevalent in middle to old age Asian. However, HBV infection is not included in the new terminology regarding whether a specific classification of HBV should be or not. Accumulating data suggested that fatty liver and obesity facilitated higher chance of HBV surface antigen clearance and lower risk of cirrhosis and HCC in natural course\textsuperscript{18} and during antiviral therapy.\textsuperscript{19} By contrast, coincidence of fatty liver and metabolic dysfunction increased the risk of hepatocellular carcinoma.\textsuperscript{20} Again, the interplay between HBV and SLD/MASLD should not be ignored from clinical practice.

From the perspectives of endocrinologists, the cardiometabolic risk threshold to determine metabolic dysfunction in SLD is discussed. As mentioned, using only one CMRF as the criteria may cause over-estimation of MASLD/MetALD and under-estimation of other types of SLD. Meanwhile, the young and lean subjects with hepatic steatosis without any metabolic risk factors will be classified as cryptogenic SLD, even if they may share the same disease pathophysiology. Concerning the treatment of MASLD, therapeutic agents that are effective in metabolic syndrome may reverse MASLD. Same as for NAFLD/MAFLD, lifestyle modifications are the cornerstone but are challenging for most patients. The glucose-lowering agents, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide 1 (GLP
1) receptor agonists have been shown to improve steatohepatitis and reduce cardiovascular risk. Thus, they may be applied in treating MASLD, especially with type 2 diabetes. In the last part, the interaction between insulin resistance and alcohol consumption is discussed. It is uncertain regarding the safe alcohol amount due to the individual genetic differences and the relative contributions of metabolic dysfunction and alcohol to MetALD disease progression.

To conclude, Kim et al. reviewed the new terminology of SLD and its subclassifications, the advantages and insufficiencies of the new terminology. As mentioned, future research is encouraged for the new biomarkers and drugs for MASLD. Further explorations regarding the natural course and disease prognosis of the subtypes of SLD, especially MASLD, MetALD and concomitant of viral hepatitis, are also necessary.
**Reference**


12. Schneider KM, Schneider CV. A new era for steatotic liver Disease: Evaluating


