Letter to the Editor

JOURNAL
OF HEPATOLOGY

Reframing the spectrum of steatotic liver disease as a dynamic concept

To the Editor:

Historically, liver diseases characterized by the accumulation of steatosis within hepatocytes have been categorized into distinct clinical entities, primarily non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ALD).[1,2] This traditional approach created rigid boundaries that defined NAFLD by the absence of significant alcohol consumption and, conversely, attributed ALD exclusively to excessive alcohol consumption, thereby segregating these liver diseases into distinct clinical and research silos. Consequently, scientific inquiries, clinical strategies, and research funding streams for NAFLD and ALD developed independently, further reinforcing the silo approach.

Since the original definition and nomenclature of NAFLD did not connect the name to an underlying metabolic abnormality or the presence of cardiometabolic risk factors (CMRFs)[2] and since the term "fatty" may carry/convey potential stigma, the new consensus nomenclature 'steatotic liver disease (SLD) was adopted as a pivotal shift.[3] This new SLD framework created three distinct clinical entities: metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic and alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD).[3] However, a significant amount of overlap has been noted between these liver diseases. This perspective is supported by recent data suggesting that some patients with MASLD may under report their alcohol consumption and, in fact, consume significant amounts of alcohol as determined by phosphatidylethanol (PEth) testing. For instance a study of over 6,000 patients with presumed MASLD showed that 20% of them had PEth levels consistent with MetALD and 13% had values consistent with ALD.[4] Another study found that 17.2% of people with a MASLD diagnosis either had a prior or a follow-up diagnosis of ALD or of alcohol use disorder.[5] Finally, a recent Danish prospective study of nearly 3,000 people at risk of SLD found that 39% of patients with MASLD could be reclassified as MetALD or ALD when using the ≥20 and ≥200 ng/ml cut-offs for PEth.[6] These data may help explain the so-called 'SLD burden paradox': while MASLD is 10 times more prevalent than MetALD and ALD, the latter account for greater global liver-related morbidity and mortality.[1]

In addition to the mislabelling of MASLD, there is a significant interaction between ALD and CMRFs; the vast majority of patients with ALD have at least one CMRF. Presence of CMRFs in patients with ALD can be attributed not only to the high prevalence of obesity and type 2 diabetes (T2D) in the general population, but can also be driven by alcohol itself, causing weight gain, hypertension, dyslipidemia, and insulin resistance.[7,8] Therefore, finding patients with pure ALD (no CMRF) is uncommon.[9]

In addition to the variable clinical characteristics of patients with SLD, there is evidence that the outcomes of these patients do not follow a predictable linear path.[10] Although some of the variabilities in disease progression can be ascribed to underlying genetics, environmental factors – mostly related to diet, body weight, and alcohol consumption – can impact the severity of CMRFs and therefore liver disease progression.[4] This variability in disease progression and regression is reflected in MASLD clinical trials in which a high proportion of patients in the placebo arm may achieve spontaneous regression of fibrosis, referred to as the "placebo effect".[10,11] While lifestyle and weight changes during the trial may be responsible for this improvement, it is also likely that underrecognized changes in alcohol consumption, which can be captured by biomarkers such as PEth, could have changed over time, influencing the course of liver disease. To date, changes in PEth values during MASLD clinical trials and their impact on histologic endpoints, have not been described.

We propose that the current evidence suggests that SLD is not a static disease with three fixed categories, but rather a dynamic and overlapping spectrum depending on the amount of alcohol consumed or the control of co-existing metabolic abnormalities over time (Fig. 1). This concept has important implications for prevention, clinical management, and clinical trials. In primary prevention, there is an urgent need to simultaneously reduce exposure to alcohol and unhealthy food, and to actively promote food and alcohol advocacy and policy changes. At the secondary prevention level (early detection), high-risk groups should be defined considering the moving parts of the puzzle and the dynamic balance between risk factors (alcohol and CMRFs). For tertiary prevention (prevention of progression and complications of the liver disease) – the pathways of care should be tailored to the patients' characteristics and needs, and interacting risk factors should be managed by interdisciplinary teams. As for clinical trials, since spontaneous improvement in lifestyle during the clinical trial may occur due to increased clinical monitoring and patient motivation, it is essential to document changes in CMRFs and alcohol consumption using validated markers periodically during the trial.[12] This would control for potential confounding effects and allow treatment strategies to be tailored to individual patients, since the balance between risk factors may change the response to treatment (interaction = effect modification). This is also relevant to phase IV (post-marketing) analyses, which will determine the ultimate impact of new drug regimens for SLD in real-world practice.

In conclusion, breaking the artificial silos of MASLD, MetALD and ALD in favour of the dynamic spectrum of SLD is essential, not merely for semantic clarity, but for advancing patient-centred care, refining risk assessment and devising individual treatment strategies. It is time to recognise the respective impact of alcohol and metabolic

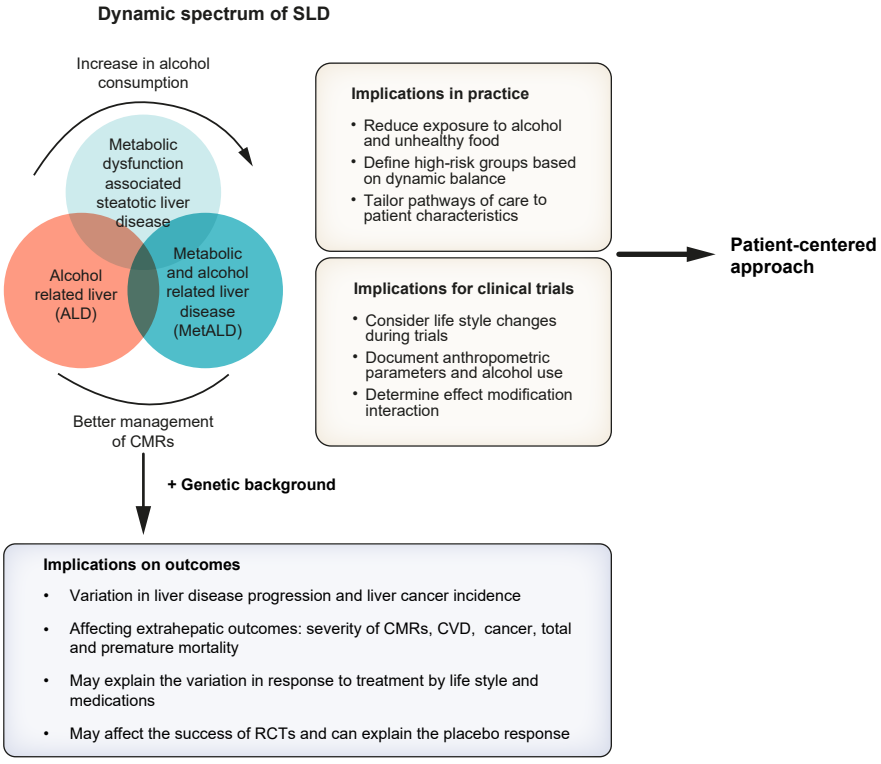

Fig. 1. Dynamic spectrum of SLD.

factors, and the way their balance may change over time, to more accurately comprehend the interconnected and dynamic nature of SLD.

Zobair M. Younossi[1,2,*]
Shira Zelber-Sagi[1,3]
Aleksander Krag[1,4]
[1]*The Global NASH Council, Washington DC, United States*
[2]*Beatty Liver and Obesity Research Program, Inova Health System, Falls Church, VA, United States*
[3]*School of Public Health, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel*
[4]*Centre for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, Odense 5000, Denmark*
[*]Corresponding author. Address: The Global MASH Council, Center for Outcomes Research in Liver Diseases, 2411 I Street, Washington DC 20037, United States; Tel.: (703) 283-1638.
E-mail address: Zobair.Younossi@cldq.org (Z.M. Younossi)

Received 26 June 2025; Accepted 27 June 2025; Available online xxx
https://doi.org/10.1016/j.jhep.2025.06.026

Financial support

This letter was partially funded by the Global NASH and the Global Liver Councils, the Beatty Center for Liver and Obesity Research and the Center for Outcomes Research in Liver Disease.

Conflict of interest

Zobair M. Younossi is a consultant or has received research funding from Intercept, Cymabay, Boehringer Ingelheim, Ipsen, Gilead Sciences, Inventiva, BMS, GSK, NovoNordisk, Siemens, Madridgal, Merck, Akero and Abbott. All other authors have no conflicts of interest to declare relevant for this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Zobair M. Younossi-study design, critical writing and editing of the manuscript. Shira Zelber-Sagi-study design, critical writing and editing of the manuscript. Aleksander Krag -study design, critical writing and editing of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2025.06.026.

References

Author names in bold designate shared co-first authorship

[1] Torp N, Israelsen M, Krag A. The steatotic liver disease burden paradox: unravelling the key role of alcohol. Nat Rev Gastroenterol Hepatol 2025;22:281–292.
[2] Matteoni CA, Younossi ZM, Gramlich T, et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413–1419.
[3] Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79:1542–1556.

[4] Vaz J, Nasr P, Helander A, et al. Phosphatidylethanol levels distinguish steatotic liver disease subgroups and are associated with risk of major liver outcomes. J Hepatol 2025;12. https://doi.org/10.1016/j.jhep.2025.04.019. S0168-8278(25)00246-6.

[5] Nasr P, Wester A, Ekstedt M, et al. Misclassified alcohol-related liver disease is common in presumed metabolic dysfunction-associated steatotic liver disease and highly increases risk for future cirrhosis. Clin Gastroenterol Hepatol 2024;22:1048–1057 e1042.

[6] Bech KT, Torp NC, Schnefeld HL, et al. Discrepancies between self-reported alcohol intake and phosphatidylethanol in 2,925 individuals at risk of steatotic liver disease. J Hepatol 2025;82(S1). S28–S28.

[7] Israelsen M, Juel HB, Detlefsen S, et al. Metabolic and genetic risk factors are the strongest predictors of severity of alcohol-related liver fibrosis. Clin Gastroenterol Hepatol 2022;20:1784–1794 e1789.

[8] **Arab JP**, **Diaz LA**, **Rehm J**, et al. Metabolic dysfunction and alcohol-related liver disease (MetALD): position statement by an expert panel on alcohol-related liver disease. J Hepatol 2025;82:744–756.

[9] Israelsen M, Torp N, Johansen S, et al. Validation of the new nomenclature of steatotic liver disease in patients with a history of excessive alcohol intake: an analysis of data from a prospective cohort study. Lancet Gastroenterol Hepatol 2024;9:218–228.

[10] De A, Keisham A, Duseja A. Letter to the editor: spontaneous regression of cirrhosis: a paradigm shift in our understanding of the natural history of NASH. Hepatology 2022;76:E1–E2.

[11] **Ng CH**, **Xiao J**, **Lim WH**, Chin YH, Yong JN, Tan DJH, et al. Placebo effect on progression and regression in NASH: evidence from a meta-analysis. Hepatology 2022;75:1647–1661.

[12] Pais R, Cariou B, Noureddin M, et al. A proposal from the liver forum for the management of comorbidities in non-alcoholic steatohepatitis therapeutic trials. J Hepatol 2023 Sep;79(3):829–841. https://doi.org/10.1016/j.jhep.2023.03.014. Epub 2023 Mar 29. PMID: 37001695.