MASH Redefined: Insights from the EASL Congress 2025

Authors:	Kayleigh Thirlwell,[1] *Lara Campana[1,2] 1. Resolution Therapeutics Ltd, Edinburgh, UK 2. University of Edinburgh, UK *Correspondence to lara.campana@resolution-tx.com
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THE EUROPEAN Association for the Study of the Liver (EASL) Congress 2025, Amsterdam, the Netherlands, placed patients and the public at the heart of its agenda, emphasising the importance of liver health through early detection, prevention, and improved access to emerging treatments. The meeting served as a strategic inflection point to assess real-world data and address the implications of the newly adopted steatotic liver disease (SLD) nomenclature. This feature distils the key emerging themes from the congress, spanning public engagement, policy change, implications of the new SLD framework, and clinical data from repurposed drugs to target a wider patient population.

EARLY DETECTION, PUBLIC ENGAGEMENT, AND AFFECTING POLICY CHANGE

Undiagnosed liver fibrosis remains a major public health challenge. Results from the LIVERSCREEN cohort (30,541 participants) revealed a high prevalence of elevated liver stiffness (>8 kPa) primarily linked to SLD driven by metabolic risk factors and high-risk alcohol use. Hospital referrals were made for 8% of participants, and 32% of those were diagnosed with chronic liver disease with fibrosis, a total of 782 individuals.[1] These findings underscore the urgent need for early detection to prevent advanced liver disease, where treatment options are limited.

Public interest in liver health is growing, as seen by the long lines of individuals eager to check their liver health at the conference. This highlights both rising awareness and limited access to testing.

The 2025 EASL Congress reaffirmed its call to recognise SLD as a non-communicable disease and to prioritise liver health within national and international health agendas by aiming to tackle Europe's alcohol burden. Despite clear evidence linking alcohol to liver morbidity and mortality, policy action remains inconsistent.

The message at EASL 2025 was clear: to bridge the gap between science and care, researchers, clinicians, and policymakers must act together. Evidence-based interventions like alcohol pricing, labelling reforms, and raising the legal drinking age were suggested tools to reduce harm.

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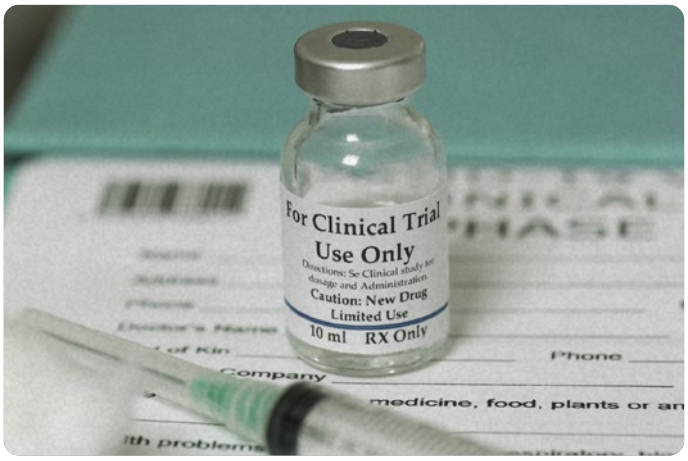
UNTANGLING LIVER DISEASE: IMPLICATIONS FOR TRIALS AND CARE

The recent reclassification of liver diseases into metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD) has presented both clarity and complexity for clinical trial design. While MASLD is now defined by the presence of steatosis and metabolic dysfunction, MetALD and ALD introduce overlapping aetiologies, particularly where alcohol consumption coexists with metabolic risk. Despite alcohol's well-established role in liver pathology, only 2–5% of reported cases fall under ALD or MetALD, which is grossly unrepresentative of global alcohol exposure. Correcting for underreporting using tools such as AUDIT-C and longitudinal phosphatidylethanol (PEth) testing suggests that up to 50% of patients currently categorised as MASLD may meet criteria for MetALD, highlighting the urgent need for more accurate patient stratification. This diagnostic fluidity complicates trial recruitment and endpoint interpretation. In one study, 38% of patients with MASLD and over 60% of those with MetALD or ALD changed categories based on alcohol intake and steatosis status.[2] Given this variability, a combined approach using non-invasive tests (NIT) and validated alcohol screening tools is essential to stratify patients reliably.

From a therapeutic perspective, shared pathogenesis between metabolic dysfunction-associated steatohepatitis (MASH) and alcohol-related liver diseases offers a rationale for drug repurposing. Drugs with a mechanism of action that have the potential to target both MASH and ALD, such as thyroid hormone receptor beta (THR-β) agonists, glucagon-like peptide-1 (GLP-1) receptor agonists, and fibroblast growth factor 21 (FGF-21) analogues, are now under investigation across these categories. For instance, MASH drugs are being trialled in ALD, and peroxisome proliferator-activated receptor (PPAR) agonists and hydroxysteroid 17-beta-dehydrogenase 13 (HSD17B13) inhibitors are being evaluated for efficacy in MetALD and ALD, with early trends showing promise in fibrosis markers.

To this end, strategic trial design will ensure that medicines reach more patients in an efficient and cost-effective way. Some suggestions included basket trial designs encompassing MASLD, MetALD, and ALD, or hybrid designs that cluster MASLD with MetALD, or MetALD with ALD. Regardless, safety remains a concern; alcohol may increase gut permeability and affect oral drug solubility, impacting both efficacy and tolerability.

Considering the shift in trial design from a regulatory standpoint, the evolving terminology necessitates clarity in inclusion criteria, biomarker-based endpoints, and justification of population definitions, especially for therapies aiming for broad SLD indications. To this end, it is encouraging to see that real world data is supporting the move from needing liver biopsies to non-invasive tests for diagnosis (LITMUS consortium)[3] and endpoints (HARMONY Trial).[4] This is a welcome step in reducing the biopsy bottleneck, and it highlights the need to develop a new reasonably likely surrogate endpoint. However, with fewer trials now relying on liver biopsies, there is a growing reliance on NITs; yet no single NIT reliably identifies both fibrosis and steatohepatitis across the SLD spectrum. Despite the challenges, the collective shift from biopsies to NITs reflects an interdisciplinary, patient-centered approach being adopted by both drug developers and clinicians.



CLINICAL EVIDENCE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS CIRRHOSIS

At the EASL Congress 2025, several investigational agents demonstrated potential in improving fibrosis and reducing portal hypertension in patients with compensated MASH cirrhosis (F4c):

- Resmetirom (MAESTRO-NAFLD-1):[5,6] Two-year open-label data showed sustained improvements in liver stiffness, fibrosis biomarkers, and portal hypertension risk, with good tolerability, supporting its clinical potential ahead of outcome data from MAESTRO-NASH OUTCOMES.
- Efruxifermin (SYMMETRY):[7] First randomised controlled trial to show histologic reversal of cirrhosis due to MASH with a 96-week treatment, along with NIT and metabolic improvements, reinforcing its antifibrotic and metabolic efficacy.
- Belapectin (NAVIGATE): While the primary endpoint was not met, 2 mg dosing significantly reduced new varices and improved liver stiffness in a per-protocol analysis, suggesting delayed portal hypertension progression; extended 36-month data are awaited (unpublished; NCT04365868).[8]

CONCLUSION

EASL 2025 has paved the way for future efforts by highlighting some key themes:

1. Undiagnosed fibrosis is a major health issue, with real-world data supporting the urgent need for early detection tools.
2. Despite public awareness of the importance of liver health, there is a strong need for evidence-based policy reform to tackle alcohol-related liver damage, an action that EASL and partners are actively pursuing.
3. In the context of MASLD, MetALD, and ALD, patient stratification remains a challenging and dynamic situation.
4. Alternative trial designs, such as basket trials and the promise of large omics and AI, could offer a viable path forward for accelerating drug development across the spectrum of SLD.
5. Drugs are reaching more patients, whether they are being repurposed from patients with MASH to patients with MetALD or ALD, or from patients with MASH to those with compensated MASH cirrhosis.

“At the EASL Congress 2025, several investigational agents demonstrated potential in improving fibrosis and reducing portal hypertension”

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