MASLD

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Clusters of metabolic dysfunction-associated steatotic liver disease for precision medicine

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a heterogeneous disease regarding its pathophysiology and clinical outcomes. Two novel studies suggest that different clusters of people with MASLD exist, explaining part of this heterogeneity. These findings and future research applying data dimensionality reduction approaches might be beneficial for implementing precision medicine in MASLD.

REFERS TO Raverdy, V. et al. Data-driven cluster analysis identifies distinct types of metabolic dysfunction-associated steatotic liver disease. *Nat. Med.* **30**, 3624–3633 (2024); Jamialahmadi, O. et al. Partitioned polygenic risk scores identify distinct types of metabolic dysfunction-associated steatotic liver disease. *Nat. Med.* **30**, 3614–3623 (2024).

Metabolic risk factors such as unhealthy diets, a lack of physical activity and genetic risk often induce increased blood pressure, blood glucose and lipid levels, as well as obesity, promoting the non-communicable diseases cardiovascular diseases (CVDs) and type 2 diabetes (T2D). Importantly, the same risk factors are also associated with metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as nonalcoholic fatty liver disease)[1–4], and MASLD is considered to be another, often unrecognized non-communicable disease[5]. Addressing the heterogeneity observed in the pathogenesis of metabolic diseases, data dimensionality reduction approaches based on clustering strategies using anthropometrics, metabolic parameters and genetics proved promising for future implementation of precision medicine in clinical practice, for example, for obesity and T2D[6]. Recently, Raverdy et al.[7] and Jamialahmadi et al.[8] suggested that such clustering strategies are also helpful in identifying distinct groups of people with MASLD with different liver and cardiometabolic disease risks and identifying yet undetected pathomechanisms of MASLD.

It is currently unclear whether the findings of these studies are important for future research in MASLD, and what roadblocks need to be overcome before the findings can be implemented in clinical practice. It is undisputed that it is critical to identify the people with MASLD who have the highest risk for MASLD-associated diseases. With more than 30% of the global adult population being affected by MASLD, the prevalence of MASLD is high and is expected to increase steadily during the next decade[9]. Although about 60–70% of the people with MASLD have steatosis without liver inflammation or fibrosis, others have hepatic inflammation (metabolic dysfunction-associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis) with or without hepatic fibrosis[1]. MASH, and particularly fibrosis, strongly increases the risk of liver disease progression, such as cirrhosis and hepatocellular carcinoma, in people with MASLD[1,4,9]. Therefore, it is crucial to identify those with MASLD who have the highest risk of developing these advanced liver diseases.

In this respect, among the six clusters identified by Raverdy et al.[7], people in clusters 2 and 5 had a high prevalence of MASH and advanced fibrosis (F ≥ 3) diagnosed by liver biopsy samples versus the other clusters combined: 33.6% and 24.2% versus 5.0%, and 21.8% and 15.8% versus 3.4%, respectively. The cardiometabolic cluster (cluster 2; adjusted HR 4.04, 95% CI 3.50–4.66, $P < 0.001$) and the liver-specific cluster (cluster 5; adjusted HR 4.52, 95% CI 3.88–5.26, $P < 0.001$), had a similarly elevated risk of chronic liver disease compared with the control cluster, comprising the clusters 1, 3, 4 and 6. Importantly, the liver-specific cluster was enriched with the MASLD at-risk genetic variants in *PNPLA3*, *TM6SF2*, *MBOAT7* and *GCKR* that are associated with increased liver disease progression to MASH, cirrhosis and hepatocellular carcinoma[1,4]. Thus, for predicting advanced liver disease, the data-driven clusters identified in this study using six variables (age, BMI, blood glycated haemoglobin, alanine transaminase, low-density lipoprotein cholesterol and triglyceride levels) cannot help largely improve the prediction of advanced liver diseases in people with MASLD[7]. Nevertheless, the approach Raverdy et al.[7] chose might be interesting for future research to identify liver-specific risks in people with MASLD. Genetic information is becoming increasingly available, and non-invasive biomarkers to detect advanced fibrosis in MASLD and MASH have effectively predicted major liver-related events[10]. Novel data-driven cluster approaches using parameters more strongly related to the liver histology phenotype than the predominantly metabolic parameters used by Raverdy et al.[7] will probably help achieve this goal.

Jamialahmadi et al.[8] specifically focused on genetic information in MASLD research. First, using multi-adiposity-adjusted genome-wide association studies, the researchers identified 17 previously unknown loci associated with liver lipid content and 9 associated with liver inflammation and fibrosis. Among them, four loci were associated with both traits. Second, the researchers investigated whether putative causal loci for liver traits exist. They found strong evidence that increased liver lipid content causes inflammation, and they also identified genetic variants involved in liver triglyceride content or liver inflammation. In addition, the researchers found liver triglyceride-increasing loci associated with decreased visceral fat mass. We consider this information

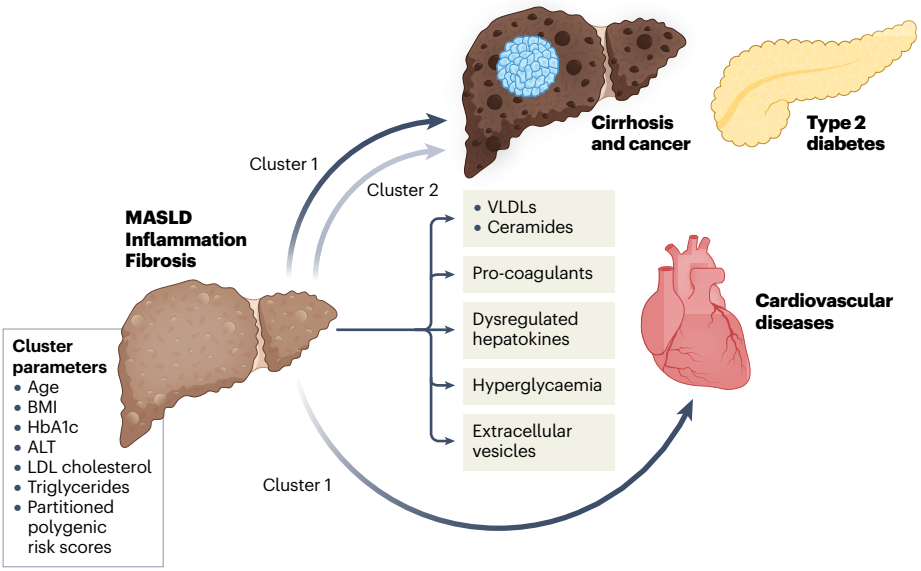

Fig. 1 | Clusters of people with MASLD. Box on the left shows the parameters that are used for clustering people with MASLD. The clusters identified with similar risk for advanced liver disease but with different risk for cardiovascular diseases, and the mechanisms involved in the crosstalk of the liver with other organs and tissues are also shown. ALT, alanine transaminase; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; VLDL, very-low-density lipoprotein.

crucial for future research on MASLD pharmacological targets. Today, several drugs are being developed to treat MASH and liver fibrosis. They mostly have different modes of action, for example, inhibition of inflammation or fibrosis, increase of liver mitochondrial function, decrease of total adipose tissue mass and increase of subcutaneous adipose tissue mass[1,10]. Thus, if the partitioned polygenetic risk scores and information about single genetic loci identified in the study by Jamialahmadi et al.[8] also prove effective for risk stratification and response to pharmacological treatment, these findings might become relevant for the management of patients with MASLD in routine clinical practice.

A milestone achieved by those two elegant studies[7,8] is identifying distinct types of MASLD that have different risks of cardiometabolic diseases, particularly CVDs. Among people with MASLD, less than 10% develop liver-related complications. The major causes of death in people with MASLD are CVDs. For example, Younossi et al.[9] found that the cause-specific mortality rate was 1.75 (95% CI 0.58–2.91) for liver-specific mortality and 5.54 (95% CI 2.72–8.35) for cardiac-specific mortality. In the study by Raverdy et al.[7], people assigned to the liver-specific cluster had a rapid progression of chronic liver disease but a relatively low risk of CVDs. People assigned to the cardiometabolic cluster, which was predominantly characterized by elevated glycaemia and high levels of blood triglycerides, had a similar incidence of chronic liver disease but an increased risk of CVDs and T2D. Analyses of liver transcriptomics and plasma metabolomics showed that these two types of MASLD clusters had distinct liver transcriptomic profiles and plasma metabolomic signatures, respectively. In agreement with these findings, Jamialahmadi et al.[8] found that people assigned to the liver-specific or so-called discordant (that is, high liver fat content but relatively low circulating triglycerides) MASLD phenotype had aggressive liver disease but a decreased risk of CVDs. The other, a systemic or so-called concordant MASLD phenotype, was also associated with a similarly increased risk of aggressive liver disease but an increased risk of CVDs and T2D (Fig. 1).

The novel findings of these two studies[7,8] support that in the future, data dimensionality reduction approaches based on clustering strategies might be effective in improving the prediction of MASLD-associated risk, similar to what is being done for obesity and T2D. However, particularly to better stratify the liver-specific risk, using liver phenotypes based on imaging and/or non-invasive MASLD-related biomarkers for cluster analyses might help to better achieve this goal. In addition, as there are some differences in MASLD pathogenesis in people with normal weight compared with people with obesity and in men compared with women, future investigation of these risk stratification approaches in subgroups of people with MASLD is necessary to implement precision medicine for MASLD in the medical guidelines and clinical practice.

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Competing interests

The authors declare no competing interests.