https://doi.org/10.1038/s44355-026-00061-3

Diversity in metabolic dysfunction-associated steatotic liver disease: a framework for precision medicine

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Metabolic dysfunction–associated steatotic liver disease (MASLD) encompasses a broad spectrum of biological and clinical variability driven by diverse genetic, metabolic, histologic, and environmental factors. In this narrative review, we synthesize current evidence on the multidimensional heterogeneity of MASLD and outline how these variations shape disease mechanisms, progression, and potential precision-medicine strategies. We integrate insights from genetic determinants with differences in histopathology, clinical phenotypes, gut microbiome signatures, and body composition to highlight how these factors may contribute to distinct disease trajectories and therapeutic responses.

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease (NAFLD), is a term used to describe a progressive form of steatotic liver disease that resembles alcohol-related steatohepatitis but was found in patients who denied alcohol misuse, and is now the most prevalent chronic liver condition, affecting more than one-third of the global adult population[1,2]. The shift in terminology is accompanied by a growing understanding of the metabolic mechanisms that drive the onset and progression of MASLD, as well as its broad phenotypic heterogeneity[3]. The spectrum of MASLD encompasses simple hepatic fat accumulation that may advance to steatohepatitis (MASH), progressive fibrosis, and potentially cirrhosis or hepatocellular carcinoma (HCC)[4]. However, disease progression in MASLD is highly variable, with patients exhibiting markedly different clinical trajectories, underscoring the need for personalized treatment strategies[5]. A key factor contributing to this variability is the spatial and temporal heterogeneity of liver involvement, which complicates accurate diagnosis, staging, and therapeutic decision-making.

Spatial heterogeneity implies that the zonal differences in hepatic lobules further increase complexity, as hepatocytes from different lobular regions perform distinct metabolic functions and vary in their susceptibility to injury[6]. For example, zone 1 is characterized by metabolic functions requiring higher oxygen tension, fatty acid β-oxidation, and gluconeogenesis, and zone 3 is characterized by detoxification, bile metabolism, and lipogenesis. Translated to MASLD, early disease stages often exhibit lipid droplet accumulation in zone 3, while later stages tend to involve zone 1. In advanced imaging, these patterns reveal a disease process that changes both across space and over time[7]. Furthermore, even within the same disease stage, subtle molecular and/or genetic aberrations can predict more rapid progression and severe tissue damage, serving as potential biomarkers for predicting clinical outcomes or treatment response[8]. The previous is just a few of the varieties that challenge the management and prognosis of MASLD; moreover, these varieties of the progression of MASLD observed in previous studies underscore the importance of a precision medicine approach for MASLD that combines clinical, histological, and multiomic data to improve risk assessment and enable targeted therapies[9,10]. Accordingly, this review aims to synthesize current evidence on the biological and clinical heterogeneity of MASLD. By integrating these diverse dimensions, we seek to provide a conceptual framework to explore the possibility of precision-based risk stratification and individualized therapeutic strategies in MASLD.-Figs. 1–3.

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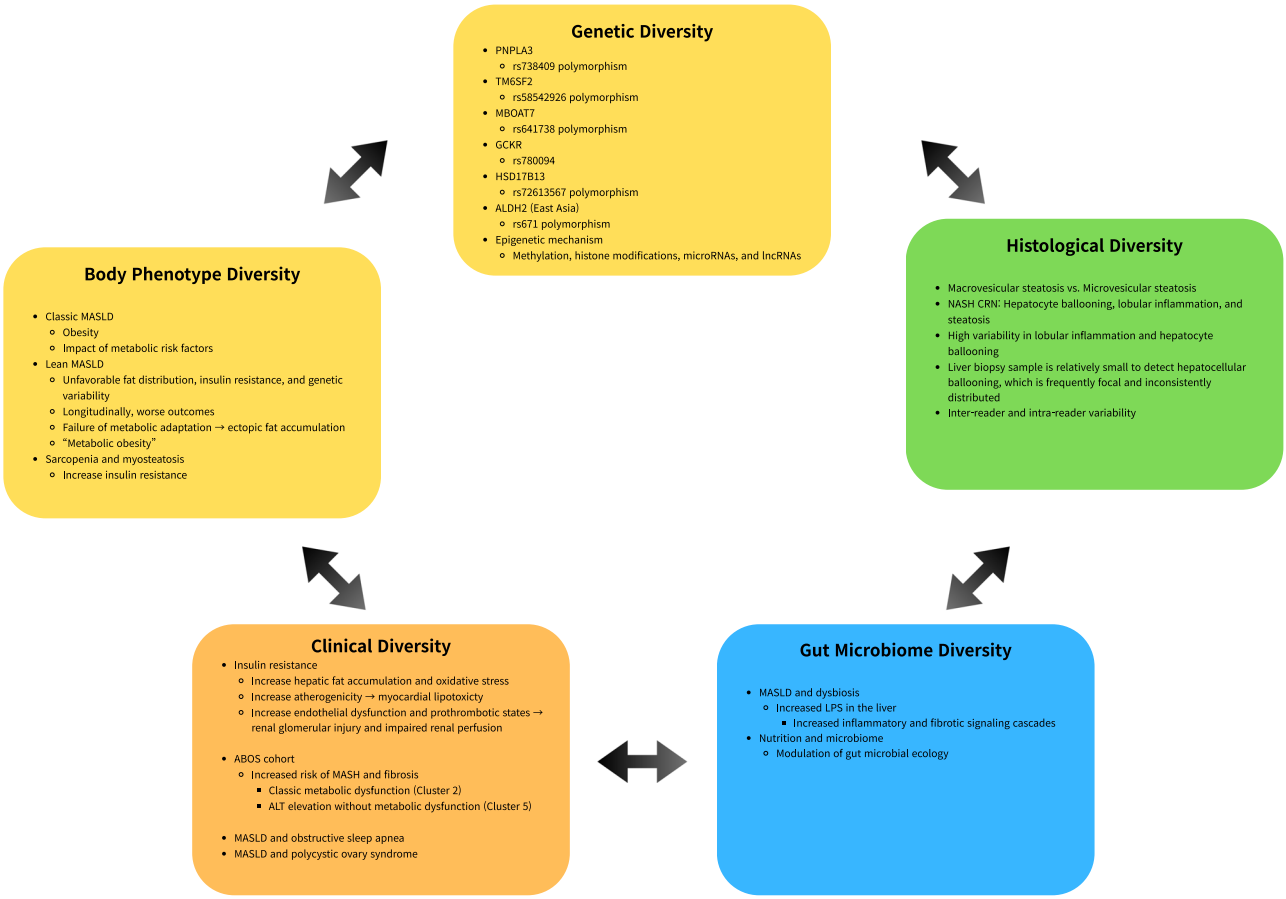

Fig. 1 | Multifactorial diversity in MASLD, highlighting genetic, phenotypic, clinical, histological, and gut microbiome variations that contribute to disease heterogeneity and progression.

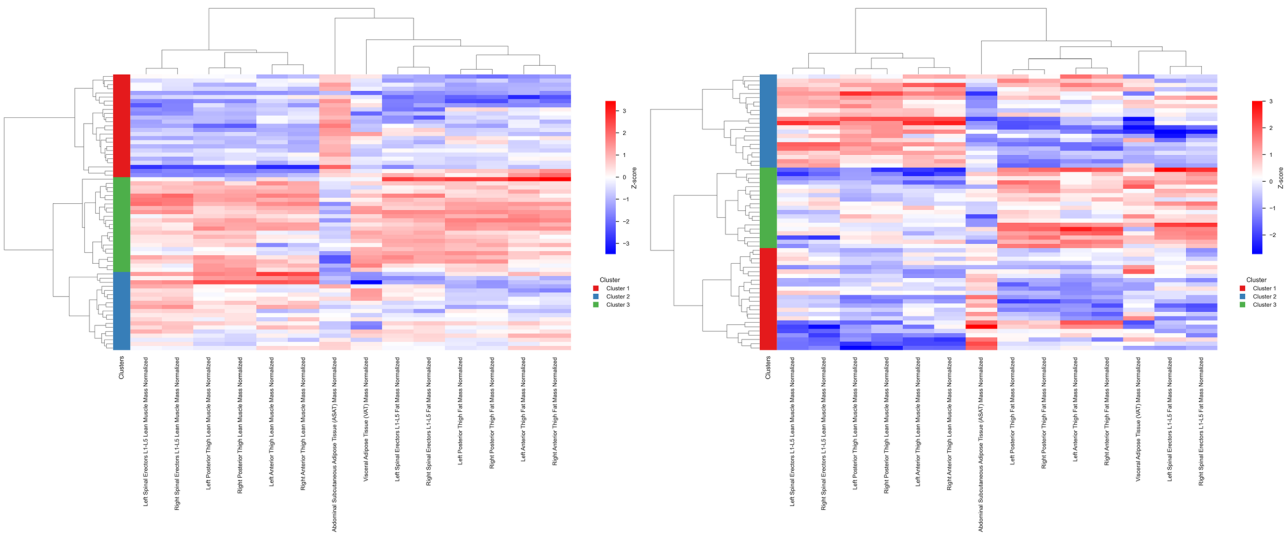

Fig. 2 | Female (left) and male (right) dendrograms showing clustering of individuals based on body composition metrics. Rows represent individuals, columns represent tissue mass variables, and color intensity reflects Z-scores (red = higher, blue = lower). *Cluster 1 is characterized by intermediate muscle and intermediate fat. Cluster 2 is characterized by high muscle and high fat, particularly marked by elevated abdominal subcutaneous adiposity. Cluster 3 is characterized by low muscle and low fat, consistent with a sarcopenic and lean phenotype.

Genetic diversity of MASLD

Common genetic variants with large effect sizes explain much of the heritability of MASLD (Table 1). The PNPLA3 p.I148M (rs738409) variant was the first identified and, due to its high allele frequency and high effect size, likely has the greatest impact at a population level[11,12]. Back in 2008, PNPLA3 was described as a gene that encodes a 481 amino acid protein of unknown function that belongs to the patatin-like phospholipase family[13]. Currently, it is widely understood that PNPLA3 is a close paralog of PNPLA2/ATGL36, the key intracellular triglyceride lipase[14–16]. The PNPLA3 was known to function as a lipase that regulates triglyceride and

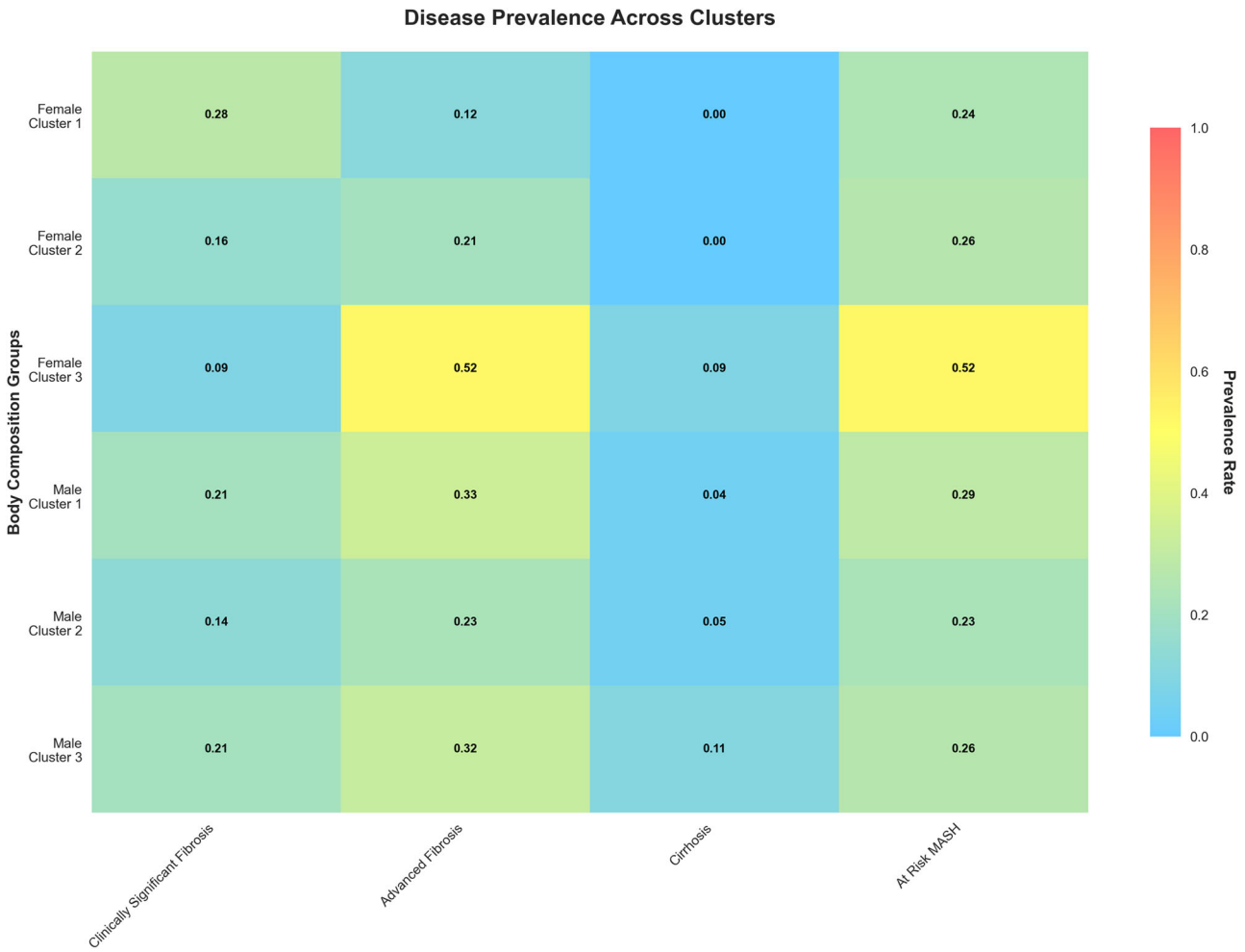

Fig. 3 | Heatmap illustrating the prevalence of liver-related conditions across sex-specific body composition clusters. Rows represent clusters (stratified by gender), columns represent liver-related conditions. The color denotes prevalence rates (red = higher, blue = lower).

Table 1 | MASLD-associated genetic variants

Gene	SNP (rsID)	Protein Change	Effect	Risk/Protection
PNPLA3	Rs738409	p.I148M	Impaired triglyceride hydrolysis ↑ hepatic fat ↑ inflammation/fibrosis	↑ Risk
TM6SF2	Rs58542926	p.E167K	↓ VLDL secretion ↑ intrahepatic lipids ↓ serum lipids	↑ Risk
MBOAT7	Rs641738	Regulatory Variant	Altered phosphatidylinositol remodeling ↑ inflammation/fibrosis risk	↑ Risk
GCKR	Rs1260326	p.P446L	↑ Hepatic glucose uptake ↑ lipogenesis ↑ steatosis ↓ fasting glucose	↑ Risk
HSD17B13	Rs72613567	Frameshift	↓ ALT/AST ↓ steatohepatitis/fibrosis risk (no effect on steatosis)	↓ Risk

PNPLA3 patatin-like phospholipase domain-containing protein 3, *TM6SF2* transmembrane 6 superfamily member 2, *MBOAT7* membrane-bound O-acyltransferase domain containing 7, *GCKR* glucokinase regulatory protein, *HSD17B13* 17β-hydroxysteroid dehydrogenase 13

retinoid metabolism in hepatocytes and hepatic stellate cells[17,18]. Newer evidence has demonstrated that PNPLA3 does not function as a major triglyceride hydrolase under physiological conditions[19,20]. The I148M substitution results in a loss of enzymatic activity and promotes accumulation of PNPLA3 on lipid droplets, where it exerts a dominant negative effect by sequestering CGI-58 and impairing ATGL-mediated lipolysis[21–24]. Furthermore, in hepatic stellate cells, the I148M substitution disrupts retinoid metabolism, contributing to stellate cell activation and fibrosis progression[25–27].This results in increased necroinflammation and fibrosis, conferring up to a 3.5-fold increased risk of advanced liver disease in an allele dose-dependent manner. Similarly, the TM6SF2, which normally functions in the endoplasmic reticulum and endoplasmic reticulum-Golgi interface to facilitate lipidation and secretion of very-low-density lipoprotein particles in both hepatocytes and enterocytes[28,29], and its p.E167K (rs58542926) variant

Table 2 | Genetic targeted MASLD/MASH randomized clinical trials

Drug Name	NCT	Targeted Gene	Key Outcome	Adverse Events
AZD2693	NCT04142424, NCT04483947, NCT05809934	PNPLA3	• Reduction of hepatic PNPLA3 mRNA and protein levels on hepatic lipid droplets Least-square mean reduction of hepatic steatosis (week 12): • −7.7% for the 25 mg dose • −12.2% for the 50 mg dose.	Well tolerated; no serious drug-related AEs; mild injection site reactions
ALN-HSD	NCT04565717 (Phase 1); NCT05519475 (Phase 2: NASHGEN-2)	HSD17B13	ALN-HSD showed robust dose-dependent reductions in HSD17B13 mRNA expression in liver biopsies. Numerically lower ALT levels over time compared with placebo. ALN-HSD group (48.6%) showed improvement in NAFLD activity score compared to placebo (22.2%) ALN-HSD group (14.3%) showed improvement in fibrosis stage compared to placebo (0%).	No serious AEs; mild-moderate injection site reactions and unrelated AEs (e.g., COVID-19)
ARO-HSD	NCT04202354	HSD17B13	Mean reduction in hepatic HSD17b13 (Day 71) • −56.9% (25 mg) • −85.5% (100 mg) • −93.4% (200 mg) Mean reduction in hepatic HSD17b13 protein levels (Day 71) • >-33.8% (25 mg) • >-86.0% (100 mg) • -83.0% (200 mg) Reductions in ALT were dose-dependent between the 25 and 100 mg dose levels, with similar reductions at the 100 and 200 mg dose levels AST reductions were similar to ALT, showing a dose-dependent decrease No clear reduction in hepatic steatosis, liver stiffness.	Well tolerated in Phase 1; no major AEs reported

PNPLA3 patatin-like phospholipase domain-containing protein 3, *HSD17B13* 17β-hydroxysteroid dehydrogenase 13

disrupts lipid secretion, leading to intrahepatic lipid buildup while lowering circulating lipids, which is an effect that highlights its liver-specific pathogenicity[30,31]. Another gene implicated in a higher propensity of developing MASLD has been the MBOAT7 and its rs8736 polymorphism (rs641738). Normally, MBOAT7 regulates the metabolic-epigenetic axis to regulate TLR-induced inflammatory responses, and these effects are further regulated by the rs8736 variant in the gene by lower MBOAT7 expression[32]. The latter leads to increased TLR dysregulation in addition to increased triglyceride synthesis, which causes hepatic inflammation and fibrosis[33,34]. Furthermore, genetic variants (PNPLA3, TM6SF2, and MBOAT7 (rs641738)) could co-exist, leading to synergistic effects, and these significantly exacerbate steatohepatitis and fibrosis beyond the impact of individual variants, as seen across diverse ancestries[12,35]. Comparably, risk of progression from steatosis to MASH and fibrosis is decreased by the loss-of-function variants in HSD17B13 (e.g., rs72613567:TA) by reducing hepatocyte lipotoxicity through altered retinol metabolism[36,37].

An emerging genetic determinant in East Asian populations is the ALDH2 Glu504Lys (rs671) variant, which impairs acetaldehyde clearance, intensifies oxidative stress, and heightens hepatocyte vulnerability to injury. This risk is magnified by endogenous ethanol production from dysbiotic gut microbiota, particularly high-alcohol-producing *Klebsiella pneumoniae*, which together accelerate steatohepatitis and fibrogenesis, as shown in $Aldh2^{-/-}$ mouse models and human transcriptomic studies[38,39]. Large multi-ancestry GWAS have confirmed ALDH2's association with liver enzyme elevations and cirrhosis, independent of alcohol intake[39,40].

At the population level, however, the ALDH2 Glu504Lys variant is also associated with alcohol intolerance and reduced likelihood of alcohol dependence, which may partially mitigate alcohol-related liver injury in affected individuals[41,42]. Thus, ALDH2 represents a dual-effect genetic factor in MASLD, wherein intrinsic hepatic vulnerability may coexist with behavioral protection from excessive alcohol exposure. This distinction underscores the importance of incorporating ALDH2 status into risk stratification models tailored to East Asian populations while carefully separating biological susceptibility from alcohol-related behavioral effects[38,43–45].

Studies have associated phenotypes and genetic variants. For instance, a recent study conducted clustering of patients with biopsy-confirmed MASLD and identified a "liver-specific cluster" characterized by the highest ALT levels and a higher incidence of advanced liver disease than a "control" cluster (HR 4.52, 95% CI 3.88–5.26, $p < 0.001$)[46]. This specific cluster was enriched for a PRS consisting of PNPLA3, TM6SF2, MBOAT7, and GCKR (rs780094) variants. In addition to the previous study, another meta-analysis including 40 studies has shown significantly higher incidence of MALO, liver-related mortality, hepatocellular carcinoma in PNPLA3-rs738409-GG, TM6SF2-rs58542926-CT or TT, and MBOAT7-rs641738-TT genotypes[47]. These studies have shown promising results to suggest that incorporating genotyping along with clinical risk scores, such as FIB4, may improve risk stratification in patients with MASLD or risk of developing MASLD[48,49].

Pharmacological efforts based on known genetic risk variants are being actively pursued. AZD2693 is an anti-sense oligonucleotide targeted at the *PNPLA3* I148M mutation and is being tested in individuals homozygous for that mutation. In a recently completed Phase 1 trial, AZD2693 demonstrated significant reductions in hepatic PNPLA3 mRNA and protein expression, alongside a dose-dependent decrease in hepatic steatosis—7.7% with the 25 mg dose and 12.2% with the 50 mg dose[50]. Based on the finding that loss-of-function mutations in *HSD17B13* confer protection against chronic liver disease, a selective HSD17B13 inhibitor ARO-HSD is also under investigation, which significantly reduces hepatic HSD17B13 mRNA and protein levels (56.9% and 33.8%, respectively) and leads to AST and ALT reduction in a dose-dependent manner when used between 25–100 mg[51]. Another agent under investigation is Rapirosiran, which successfully reduced HSD17B13 mRNA expression, AST, and ALT; furthermore, it showed improvement in fibrosis stage compared to placebo (14.3% vs. 0%, respectively) (Table 2)[52].

Table 3 | MASLD-Associated Epigenetic Mechanisms

Mechanisms	Features
DNA methylation	Altered methylation of genes like PPARA, SREBF1, HNF4A; affects lipid metabolism, inflammation, fibrosis
Histone modification	Histone acetylation (e.g., H3K27ac) activates lipogenic/inflammatory genes; dysregulation of HDACs and HMTs
MicroRNAs	miR-122 (↓), miR-34a (↑), miR-21 (↑); regulate lipid homeostasis, apoptosis, fibrosis
Long non-coding RNAs	MEG3, H19 involved in steatosis and fibrogenesis; affect chromatin regulation

PPARA peroxisome proliferator-activated receptor alpha, *SREBF1* sterol regulatory element binding transcription factor 1, *HNF4A* hepatocyte nuclear factor 4 alpha, *H3K27ac* histone H3 lysine 27 acetylation, *HDAC* histone deacetylases, *HMT* hepatic mitochondrial triacylglycerol.

In addition to genetic variants, epigenetic changes have been implicated in the development and progression of MASLD. Epigenetic mechanisms such as DNA methylation, histone modifications, microRNAs (miRNAs), and long noncoding RNAs (lncRNAs) mediate the relationship between environmental exposures (e.g., diet, obesity, toxins) and gene expression dysregulation in patients with MASLD (Table 3)[53–55]. Specifically, in MASLD, abnormal DNA methylation patterns have been identified in genes involved in lipogenesis (e.g., *SREBF1*), insulin signaling, and inflammation. These patterns correlate strongly with fibrosis severity and disease progression[56,57]. For instance, hypomethylation of *SREBF1* enhances expression of SREBP1c, which promotes hepatic lipid accumulation, while hypermethylation of *PPARα* suppresses fatty acid oxidation[56]. On the other hand, histone modifications such as H3K9 deacetylation by SNAIL1/HDAC complexes and H3K27 acetylation by SLUG/p300 regulate chromatin structure and transcription of lipid metabolism genes, which are implicated in lipid accumulation and insulin resistance in the liver[58]. Furthermore, the depletion of macroH2A, which is a noncanonical histone variant, has been associated with increased oxidative stress and fibrosis in lean MASLD, emphasizing its protective role in maintaining genomic integrity[59,60].

MASLD pathogenesis is further mediated by non-coding RNAs. miRNAs, including miR-34a and miR-122, along with lncRNAs such as MALAT1, modulate key metabolic and inflammatory pathways in MASLD. In lean MASLD patients, elevated serum levels of miR-4488 correlate with fibrosis severity, suggesting its potential as a noninvasive biomarker[59,61]. MALAT1, which is frequently upregulated in MASH, stabilizes nuclear SREBP1c and promotes insulin resistance and lipogenesis; its genetic silencing could help restore glucose homeostasis and reduce hepatic triglyceride accumulation[62]. Autophagy-related IncRNAs (e.g., PSMG3-AS1, MIRLET7BHG) can inhibit miRNAs that target lipid-handling genes (e.g., ATG7, CPT1A) through sequestration, thereby modulating hepatic lipogenesis and stellate cell activation[62]. These ncRNAs contribute to inter-individual variability and hold translational promise for blood-based diagnostics, as supported by transcriptomic analyses of human liver biopsies[59,61].

The reversible nature of epigenetic changes is a promising area for clinical applications. Nutritional interventions such as methyl donor supplementation (e.g., folate, choline) and dietary modifications such as the Mediterranean diet can modify DNA methylation and histone acetylation landscapes, which have been shown to reduce steatosis and fibrosis in clinical studies[58,60]. Targeting epigenetic enzymes through pharmacological intervention is also being explored, including the use of DNA methyltransferase inhibitors (e.g., decitabine), histone deacetylase (HDAC) inhibitors (e.g., vorinostat), and bromodomain and extra-terminal domain (BET) inhibitors, which reduce fibrosis through decreased collagen deposition and stellate cell activation[58,63]. Moreover, the combination of epigenetic biomarkers (e.g., *SREBF1* methylation, miR-122) with non-invasive tools such as the Fibrosis-4 (FIB-4) or enhanced liver fibrosis (ELF) test could provide augmented personalized risk assessment and support an individualized therapeutic plan[57,61]. In addition, emerging epitranscriptomic regulators such as METTL3, which mediates m6A RNA methylation, are under investigation and offer new targets for therapy[62]. Overall, the expanding field of MASLD epigenetics highlights its pivotal role in disease heterogeneity and opens new paths for precision medicine.

Histological diversity of MASLD

Although MASLD is characterized by a heterogeneous histopathological spectrum, macrovesicular steatosis is generally the most prevalent subtype[64]. In contrast, microvesicular steatosis, which is characterized by diffuse small lipid vacuoles preserving nuclear position, is rare, representing approximately 10% of cases[64,65]. A recent study demonstrated that the microvesicular variant is associated with advanced fibrosis and poor prognosis, suggesting a heightened cellular response[46].

Studies have assessed disease activity in MASLD using scores to grade steatosis, inflammation, and hepatocyte ballooning as validated by the NIDDK-sponsored Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) Pathology Committee[66]. When analyzed separately, lower hepatocyte ballooning (HB1 vs. HB2) was associated with a significantly reduced risk of cirrhosis, though no clear associations were observed with other liver-related or cardiovascular outcomes. In contrast, lower lobular inflammation (LI1 vs. LI2–3) was linked to decreased risks of cirrhosis, stroke, and overall adverse outcomes[67]. However, the histological features of activity in steatohepatitis, such as lobular inflammation and hepatocyte ballooning, are highly variable in distribution within tissue and dynamic over short timescales, contributing to diagnostic and prognostic challenges. For instance, lobular inflammation ranges from minimal to moderate and may be disproportionately low even in patients with advanced fibrosis, suggesting that fibrogenesis can progress independently of overt immune activity[68]. Comparably, patients may also present with prominent inflammation and minimal fibrosis, indicating a more immune-driven phenotype[69]. Hepatocellular ballooning is frequently focal and inconsistently distributed, making it difficult to detect, especially in small biopsy samples[66,70]. In addition, one of the main challenges of liver histology is its non-negligible inter- and intra-reader variability[71]. These histological inconsistencies highlight the underlying heterogeneity of MASLD.

All together, the histologic landscape of MASLD underscores the marked heterogeneity that complicates both diagnosis and prognostication. Differences in steatosis patterns, inflammatory burden, and hepatocellular ballooning reflect distinct biological processes that may evolve independently over time, rather than a uniform, linear disease course. The often focal and fluctuating nature of these features, coupled with sampling limitations and interobserver variability, further challenges the interpretation of liver biopsy findings. These observations highlight the limitations of relying on histology alone and support the need for integrative approaches that combine pathological assessment with clinical, imaging, and molecular markers to better capture disease behavior and inform personalized management in MASLD.

Clinical diversity of MASLD

MASLD frequently occurs alongside obesity and insulin resistance, which are present in over 75% of individuals with type 2 diabetes mellitus[72–74]. Insulin resistance drives hepatic fat accumulation and the transition from simple steatosis to MASH, initially triggering compensatory increases in mitochondrial fatty acid oxidation[75–77]. However, this adaptive response diminishes over time, leading to oxidative stress and the depletion of cellular antioxidant capacity. Beyond hepatic consequences, insulin resistance exerts systemic effects, promoting chronic inflammation, dyslipidemia, and endothelial dysfunction, which are key contributors to cardiovascular

disease[78,79]. In addition to its atherogenic profile, insulin resistance promotes lipid accumulation in cardiac tissue, leading to myocardial lipotoxicity[80,81]. Importantly, these risks are not confined to individuals with obesity.

Most patients with MASLD are characterized as asymptomatic during pre-cirrhotic stages. Some of the patients might experience fatigue, malaise, or right upper quadrant discomfort[82,83]. Generally, the physical exam of patients with MASLD reveals hepatomegaly in 50-60% of cases. The prevalence of metabolic risk factors or conditions is estimated to be overweight or obesity (approximately 80%), atherogenic dyslipidemia (60-70%), prediabetes or type 2 diabetes (approximately 60%), and hypertension (approximately 50%)[82]. Metabolic risk factors likely hierarchically contribute to disease severity, influencing both hepatic and extrahepatic outcomes; however, the relative importance and specific combinations of metabolic syndrome traits that confer the greatest risk of adverse liver events and systemic complications remain incompletely defined[84].

Recent phenotypic analysis from the ABOS cohort identified six MASLD subgroups, each with unique risks for MASH and fibrosis[46]. While Cluster 2 reflected classic metabolic dysfunction with elevated HbA1c, triglycerides, and hypertension, Cluster 5 is characterized by isolated ALT elevation without evident metabolic abnormalities, suggesting a liver-centric phenotype that may represent lean MASLD, where subclinical metabolic dysfunction still drives fibrotic progression. These observations reinforce MASLD as a systemic manifestation of metabolic dysfunction, with over 85% of affected individuals meeting criteria for metabolic syndrome and facing increased risks of cardiovascular, renal, reproductive, and respiratory complications[74,85,86].

Subsequently, the extrahepatic system has been implicated in MASLD. Reproductively, MASLD affects 34–70% of individuals with polycystic ovary syndrome (PCOS) and contributes to 20–30% of their metabolic burden through androgen-mediated hepatic lipogenesis, with additional fibrotic risk in estrogen-deficient states such as menopause[85,87]. Concurrently, obstructive sleep apnea (OSA) affects over half of MASLD patients, creating a bidirectional cycle in which hypoxia-induced HIF-1α promotes hepatic lipogenesis and inflammation, while liver-derived cytokines worsen airway collapsibility[87,88]. In a recent study, the risk of developing chronic kidney disease stage 3 or greater has been noted to be significantly elevated in patients with MASLD[82,83]. This renal involvement occurs through mechanisms involving oxidative stress and systemic inflammation affecting the kidneys. Lastly, MASLD is associated with an increased risk of certain extrahepatic cancers, particularly colorectal cancer, other non-liver gastrointestinal cancers, and breast cancer, with risk increases ranging from 1.2- to 1.5-fold[82,83,89]. These complex interorgan interactions highlight the need for integrated care approaches, including screening for other associated conditions; selecting agents such as GLP-1 receptor agonists or pioglitazone for combined hepatic and cardiometabolic benefit; and adopting multidisciplinary strategies to mitigate extrahepatic complications[73,86,90].

Gut microbiome diversity of MASLD

The gut microbiome has emerged as a key regulator of MASLD progression and its diverse clinical manifestations[91,92]. Studies have demonstrated that MASLD is associated with dysbiosis, defined as reduced microbial diversity and an overrepresentation of endotoxin-producing bacteria. These changes in the microbiome impair the intestinal barrier and facilitate the passage of microbial products such as lipopolysaccharide (LPS) into the liver via the portal vein[93,94]. Once in the liver, LPS activates Toll-like receptors, particularly TLR4, on resident immune cells such as Kupffer cells, triggering inflammatory and fibrotic signaling cascades. This interaction between the gut and liver is supported by experimental models where mice lacking TLR4 were protected from diet-induced steatosis, highlighting the mechanistic role of microbial signaling in hepatic injury[95]. In human studies, specific microbiome profiles have been linked to the histological severity of MASLD, prompting interest in microbiota-modifying therapies, including probiotics, prebiotics, and fecal microbiota transplantation[92,96,97].

In MASLD, Alpha and Beta diversity are underscored as typically, MASLD has been described as reduced alpha diversity but notably distinct Beta diversity[98]. In a large population-based study, Shannon diversity was significantly lower in patients with steatosis[99]. The magnitude of reduction is relatively small, for which some studies have reported Alpha diversity to be not significant between patients with MASLD[100,101]. In contrast, Beta diversity has been a more pronounced and consistent difference between MASLD and the healthy population. In a recent study, the pairwise analysis demonstrated significant differences in bacterial communities between healthy controls vs. MASLD and MASLD vs. chronic kidney disease[102]. Subsequently, another study has identified the most abundant genera in subjects with or without MASLD, noticing a significant difference (Ruminococcus, Streptococcus, Holdemanella, Blautia, and Lactobacillus vs. Prevotella, Bacteroides, Dialister, Acidaminococcos, Alloprevotella, and Catenibacterium, respectively)[103].

Disease progression is remarkably affected by dysbiosis[104]. Gut dysbiosis occurs in the early phase of the disease and becomes more profound as fibrosis progresses with potential transformation to hepatocellular carcinoma[105]. Dysbiosis contributes to pathogenesis through multiple mechanisms, including disrupted bile acid metabolism, reduced short-chain fatty acid production, increased intestinal permeability, and endotoxin-mediated inflammation via TLR4/ NF-κB pathways[106,107]. Diet, in turn, both shapes and is shaped by the microbiome, suggesting that nutritional interventions may act, at least in part, through modulation of gut microbial ecology[91,96]. In a randomized controlled trial of 200 adults with MASLD, resistant starch supplementation lowered intrahepatic triglyceride content by 8% through gut microbiome modulation[108]. As such, a deeper understanding of the gut microbiome holds promise for improving risk stratification and developing targeted microbiota-based treatments in MASLD.

Accumulating evidence supports the gut microbiome as a central and dynamic contributor to MASLD pathogenesis, influencing hepatic inflammation, fibrogenesis, and interindividual heterogeneity observed across clinical phenotypes. Dysbiosis-associated gut-liver axis, mediated through altered intestinal permeability and microbial-associated inflammatory pathway, provides a possible link between environmental exposures, host susceptibility, and disease progression. Importantly, variability in microbial composition appears to modify metabolic risk independently of traditional factors such as adiposity, underscoring the limitations of one-size-fits-all models of MASLD. Future studies, focusing on multi-omics studies that integrate microbiome profiling with host genomics, metabolomics, and detailed dietary assessments, may enable the development of precision-based interventions, including targeted dietary strategies, microbiota-directed therapies, and personalized risk stratification tools, ultimately advancing a more individualized and mechanistically informed approach to MASLD management.

Body phenotype diversity of MASLD

MASLD is far more complex than a disease driven simply by obesity. Lean MASLD, even in people with a normal BMI, often hides metabolic problems such as excess visceral fat, insulin resistance, and genetic factors like PNPLA3 or TM6SF2 variants that promote liver fat and fibrosis. Despite appearing less severe on routine tests, these patients may face higher risks of heart disease and certain cancers over time. On the other hand, some individuals with obesity maintain relatively healthy metabolism, illustrating the so-called "obesity paradox." Altogether, these patterns show that BMI alone cannot explain disease risk, and that understanding a patient's metabolic profile, genetics, and muscle–fat composition is key to more precise management of MASLD.

Lean MASLD poses a greater challenge as it is characterized by normal BMI. Subjects with lean MASLD are frequently encountered with metabolically unfavorable fat distribution (e.g., increased visceral adipose tissue accumulation despite normal BMI), insulin resistance, and genetic variability that increases the risk of abnormal lipid deposition specifically in the liver[109,110]. Emerging evidence has linked pathogenic alleles such as PNPLA3 p.I148M (rs738409) and TM6SF2 p.E167K (rs58542926) with lean MASLD,

Table 4 | Baseline characteristics of 132 patients

Characteristic	Overall (*n* = 132)
Age, years #	44.0 (34.0–55.8)
BMI, kg/m² #	32.0 (26.0–38.9)
Sex (Female), *n*(%)	168 (51.53)
Ethnicity, n(%)	
Chinese	184 (56.44)
Malay	87 (26.69)
Indian	44 (13.50)
Others	11 (3.37)
Diabetes, *n*(%)	127 (38.96)
Hypertension, *n*(%)	148 (45.40)
Dyslipidemia, *n*(%)	157 (48.16)
History of alcohol, *n*(%)	90 (27.61)
History of tobacco, *n*(%)	91 (27.91)
Platelet (x10⁹/L) #	281.0 (224.5–322.0)
INR #	1.0 (1.0–1.0)
Creatinine (μmol/L) #	66.0 (54.8–79.0)
AST, IU/L #	37.0 (25.0–59.0)
ALT, IU/L #	52.0 (26.0–98.8)
Steatosis grade (0–3), *n*(%)	
Grade 0	30 (9.20)
Grade 1	179 (54.91)
Grade 2	53 (16.26)
Grade 3	63 (19.33)
Lobular inflammation (0–3), *n*(%)	
Grade 0	79 (24.23)
Grade 1	168 (51.53)
Grade 2	71 (21.78)
Grade 3	7 (2.15)
Ballooning (0–2), n(%)	
Grade 0	193 (59.20)
Grade 1	79 (24.23)
Grade 2	53 (16.26)
Fibrosis Numeric (0–4), *n*(%)	
Grade 1	105 (32.21)
Grade 2	53 (16.26)
Grade 3	56 (17.18)
Grade 4	25 (7.67)
Advanced Fibrosis, *n*(%)	56 (17.18)
Clinically Significant Fibrosis, *n*(%)	53 (16.26)
Cirrhosis, *n*(%)	25 (7.67)
At Risk MASH, *n*(%)	90 (27.61)

BMI Body-Mass Index, *INR* International Normalized Ratio, *AST* Aspartate Aminotransferase, *ALT* Alanine Transaminase, *MASH* Metabolic Dysfunction-Associated Steatohepatitis
Values are represented in median (I.Q.R.).

highlighting their impact in hepatic steatosis specifically in this subset of MASLD[111,112]. Although obesity is not a definitive feature, patients with lean MASLD often have at least one cardiometabolic risk factor, such as dyslipidemia or hypertension. Therefore, patients with lean MASLD might exemplify a paradoxical "metabolic obesity" which differs from the relatively metabolically healthy obesity phenotype, in which patients have obesity without typical metabolic dysfunction[89,113,114]. Although a certain degree of hepatic steatosis is observed in subjects with relatively metabolically healthy obesity, metabolic resilience is often preserved and is characterized by intact CPT1A-mediated hepatocyte mitochondrial β-oxidation and adiponectin-dominated anti-inflammatory profiles, which attenuate TGF-β1-driven fibrogenesis and reduce the risk of incident metabolic dysfunction-associated steatohepatitis by 54% compared to subjects with metabolic obesity[115–117].

Patients with lean MASLD have a subclinical course and are often found with superior cardiometabolic profiles, reduced aminotransferase levels, and milder histologic injury with diminished steatosis, lobular inflammation, and fibrosis stages[114]. However, longitudinal studies have shown worse outcomes, including non-liver-related outcomes such as cardiovascular events and extrahepatic cancers, in lean MASLD compared to non-lean counterparts[118,119]. One possible explanation lies in the initial histologic subtlety that may obscure an underlying aggressive disease process. It has been proposed that lean MASLD may result from a failure of metabolic adaptation. In lean MASLD, individuals might resist weight gain, potentially due to higher bile acid or FGF19 signaling, or distinct gut microbiota compositions, which may lead to metabolic stress resulting in ectopic fat accumulation and hepatic injury[114].

In contrast, the relatively metabolically healthy MASLD phenotype is the opposite of lean MASLD, with individuals characterized by high BMI but fewer metabolic risk factors, and a lower risk of liver disease progression. Mortality, cardiovascular events, and advanced fibrosis of the relatively metabolically healthy MASLD phenotype are similar when compared to metabolically healthy non-MASLD controls, while metabolically unhealthy MASLD patients have fourfold higher odds of fibrosis[120,121]. This highlights that obesity is not the only driving force behind MASLD outcomes; furthermore, it underscores the "obesity paradox". Individuals with lean MASLD require metabolic vigilance, while individuals with relatively metabolically healthy MASLD require lifestyle modifications to ameliorate future metabolic function decline[84,122].

Anthropometric parameters beyond traditional adiposity measures have also been investigated in MASLD. Skeletal muscle mass (SMM) has been considered an important endocrine organ for glucose utilization and secretion of myokines that mediate interaction between muscle, liver, adipose tissue, and other organs[123]. In a study by Kim et al., increased SMM was associated with reversal of hepatic steatosis[124]. While sarcopenia has long been acknowledged as prevalent among individuals with MASLD, recent evidence suggests that myosteatosis is both common and substantially more prevalent than sarcopenia[125]. Multiple modalities were proposed to detect myosteatosis, including dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), and cross-sectional imaging (CT or MRI). Subsequently, reduced SMM contributes to an increased risk of insulin resistance[126].

Body phenotype diversity highlights the profound heterogeneity of MASLD that extends well beyond conventional BMI-based definitions. While lean MASLD underscored a paradoxical phenotype in which normal body weight conceals adverse visceral adiposity and impaired metabolic adaptability, the relatively metabolically healthy MASLD phenotype illustrates the dissociation between obesity and disease severity. Such findings lead to the conclusion that metabolic health, rather than adiposity alone, is a dominant determinant of outcomes. Future studies should prioritize longitudinal phenotyping that integrates advanced anthropometrics, body composition imaging, genetic risk profiling, and metabolic biomarkers to refine risk stratification across MASLD subtypes. Such efforts may inform tailored surveillance strategies and phenotype-specific interventions.

Cohort analysis of muscle mass in MASLD

Cross-sectional phenotypic measures across 132 individuals. Supporting evidence of body phenotypes in MASH, MRI was performed on 132 patients using AMRA® Profiler (AMRA Medical AB, Linköping, Sweden)[82]. The AMRA protocol utilized a standardized two-point Dixon imaging sequence across 1.5 T and 3 T MRI platforms, employing

Table 5 | Disease outcomes based on hierarchical clusters

Male		Female	
Advanced Fibrosis		**Advanced Fibrosis**	
Cluster 2	OR 0.59 (95% CI: 0.16–2.18, $P = 0.638$)	Cluster 2	OR 1.96 (95% CI: 0.38–10.03, $P = 0.691$)
Cluster 3	OR 0.92 (95% CI: 0.25–3.34, $P = 1.000$)	Cluster 3	OR 8.00 (95% CI: 1.86–34.36, $P = 0.007$)
At Risk MASH		At Risk MASH	
Cluster 2	OR 0.71 (95% CI: 0.19–2.70, $P = 0.872$)	Cluster 2	OR 1.13 (95% CI: 0.29–4.46, $P = 1.000$)
Cluster 3	OR 0.87 (95% CI: 0.23–3.34, $P = 1.000$)	Cluster 3	OR 3.45 (95% CI: 1.01–11.81, $P = 0.086$)
Cirrhosis		Cirrhosis	
Cluster 2	OR 1.10 (95% CI: 0.06–18.64, $P = 1.000$)	Cluster 2	OR 1.31 (95% CI: 0.02–68.87, $P = 1.000$)
Cluster 3	OR 2.71 (95% CI: 0.23–32.34, $P = 0.833$)	Cluster 3	OR 5.93 (95% CI: 0.27–130.34, $P = 0.504$)
Clinically Significant Fibrosis		Clinically Significant Fibrosis	
Cluster 2	OR 0.60 (95% CI: 0.13–2.87, $P = 0.800$)	Cluster 2	OR 0.48 (95% CI: 0.11–2.18, P = 0.552)
Cluster 3	OR 1.01 (95% CI: 0.23–4.45, $P = 1.000$)	Cluster 3	OR 0.24 (95% CI: 0.05–1.33, P = 0.180)

Cluster 1 (reference): Intermediate muscle and intermediate fat. Cluster 2: High muscle and high fat, particularly marked by elevated abdominal subcutaneous adiposity. Cluster 3: Low muscle and low fat, consistent with a sarcopenic and lean phenotype.

symmetrical chemical shift imaging to differentiate fat and water signals. The scanning protocol is based on symmetrical chemical shift imaging, specifically "Two-point Dixon" imaging, which enables rapid whole-body assessment with the commercially available service AMRA® Profiler, which automatically labels fat and muscle regions and quantifies fat and muscle volumes. The AMRA system provides automated quantification of adipose tissue compartments, muscle volumes, and muscle tissue composition with established between-scanner reproducibility and within-scanner repeatability[83]. The study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB Ref: 2016/00580).

Measures of anterior and posterior thigh mass, abdominal adipose tissue mass, visceral adipose tissue mass, abdominal subcutaneous adipose tissue mass, and spinal erector tissue mass were included in the study. These measurements represented the individual components of muscle and fat across the human body. Participants were first separated by gender (male/female) to account for natural phenotypic differences[84], and measurements were then divided by body weight to account for inter-individual differences in overall body size and were finally normalized to prevent variables with larger absolute values from dominating the clustering algorithm[85]. The clustering methodology employed agglomerative hierarchical clustering with Ward's linkage criterion and Euclidean distance metric. Agglomerative hierarchical clustering is an unsupervised machine learning technique that begins by treating each individual observation as its own cluster. Ward's method minimizes within-cluster variance at each merging step, producing compact and well-separated clusters. For each analysis, optimal cluster numbers were determined through visual inspection of the dendrograms. Four conditions were analyzed across clusters: At Risk MASH, Advanced Fibrosis, Cirrhosis, and Clinically Significant Fibrosis. Disease prevalence rates were calculated for each cluster, and cluster composition was characterized using mean normalized ratios.

Statistical analysis was conducted to evaluate whether disease prevalence differed significantly across clusters within gender-specific subgroups. For each disease condition, comparisons were made between Cluster 1 (reference) and all other clusters using odds ratios with 95% confidence intervals. P-values were derived from chi-square tests on 2×2 contingency tables[86]. A significant result indicates that the clustering was associated with differential disease prevalence, suggesting non-random structure in the data.

Results of Hierarchical Clustering in 132 individuals. The study included 132 participants with a median age of 44.0 years (IQR 34.0–55.8) and a median BMI of 32.0 kg/m² (IQR 26.0–38.9). Slightly more than half were female (51.5%), and the majority were of Chinese ethnicity (56.4%), followed by Malay (26.7%), Indian (13.5%), and other ethnicities (3.4%). Comorbid conditions were common, with 38.9% having diabetes, 45.4% hypertension, and 48.2% dyslipidemia. Histological analysis showed that steatosis was present in most participants, with 54.9%, 16.3%, and 19.3% for grade 1-3 steatosis, respectively, while only 9.2% had no steatosis. Fibrosis was observed in varying degrees: 32.2%, 16.3%, 17.2%, and 7.7% for F1-F4, respectively. At-risk MASH was present in 27.6% of the cohort (Table 4).

Females: Cluster 1 demonstrated intermediate muscle and intermediate fat. Cluster 2 exhibited high muscle and high fat, particularly marked by elevated abdominal subcutaneous adiposity. Cluster 3 was characterized by low muscle and low fat, consistent with a sarcopenic and lean phenotype (supplementary material 1). There was a statistically significant association between clusters for advanced fibrosis among females, with Cluster 3 exhibiting significantly higher odds of advanced fibrosis compared to Cluster 1 (OR = 8.00, 95% CI: 1.86–34.36, $p = 0.007$, Table 5). Additionally, there was a trend toward significance for at-risk MASH, with Cluster 2 showing increased odds compared to Cluster 1 (OR = 3.45, 95% CI: 1.01–11.81, $p = 0.086$). **Males:** Cluster 1 males exhibited high muscle and high fat, particularly in the subcutaneous abdominal regions. Cluster 2 showed intermediate muscle and low fat. Cluster 3 demonstrated low muscle and intermediate fat, consistent with a sarcopenic profile (Supplementary Table 1). No statistically significant associations were found between cluster membership and disease outcomes among males.

Conclusion

MASLD represents a heterogeneous spectrum of liver injury shaped by genetic predisposition, clinical comorbidities, nutritional factors, microbial alterations, and body composition. Advances in studies have suggested the impact of genetic predisposition, leading to rapid progression in patients with MASLD. This variety of MASLD presentations highlights the complexity of MASLD and underscores the need for individualized risk stratification and tailored therapeutic strategies other than weight management. Newer pharmacological agents have shown promising results and might provide an improved treatment plan in the future. Although several aspects of MASLD pathophysiology remain poorly understood, this review provides an up-to-date synthesis of current evidence to advance clinical insight into its variable progression and to guide future approaches to management.

Data availability

No datasets were generated or analysed during the current study.

Received: 28 July 2025; Accepted: 10 February 2026;
Published online: 04 June 2026

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Acknowledgements

Authors have no funding to declare.

Author contributions

Donghyun Ko, Jordan Low, and Peter Low conceived the review topic, designed the overall structure, performed the literature search, extracted data, and drafted the initial manuscript. Cheng Han Ng contributed to literature synthesis, data organization, figure development, and critically revised the manuscript. Damien Chua supported data interpretation, refined the conceptual framework, and contributed to manuscript editing. Vincent Chen, Jonathan A. Fallowfield, Timothy J. Kendall, Hirokazu Takahashi, Cheng Han Ng, Nicholas Syn, and Mark Muthiah provided senior oversight and expert critical review of the manuscript. They contributed domain expertise in hepatology, clinical interpretation, and ensured scientific rigor and alignment with current evidence. Cheng Han Ng, Nicholas Syn, and Mark Muthiah additionally provided guidance on manuscript organization, clinical relevance, and intellectual content development. All authors reviewed and approved the final version of the manuscript. Donghyun Ko, Jordan Low, and Peter Low contributed equally to this work and share first authorship.

Competing interests

Mark D. Muthiah: M.D.M has served as a consultant to Roche, Estella, and Gilead. He has been an advisor for LernaBio. M.M has received payment from speaking at Boston Scientific, Olympus Medical, Roche, and Astellas. He also serves as the CMO of LiverGENIX PTE LTD. M.D.M is supported by the Singapore Ministry of Health through the National Medical Research Council (NMRC) Office, MOH Holdings Pte Ltd under the NMRC Clinician Scientist-Individual Research Grant (MOH-001228) and NMRC Clinician Scientist Award (MOH-001631), as well as the National Research Foundation, Singapore (NRF) under the NMRC Open Fund – Large Collaborative Grant (MOH-001325) and administered by the Singapore Ministry of Health through the NMRC Office, MOH Holdings Pte Ltd. Cheng Han Ng: C.H.N serves as the CEO of LiverGENIX Pte Ltd. Nicholas Syn: N.S serves as the CTO of LiverGENIX Pte Ltd Hirokazu Takahashi: H.T has received research grants from Astellas Pharma, AbbVie GK, and Sysmex. Vincent Chen: VLC received research grants from AstraZeneca, KOWA, and Ipsen, paid to the University of Michigan. Jonathan A. Fallowfield: J.A.F serves as a consultant and/or advisory board member for Resolution Therapeutics, Kynos Therapeutics, Ipsen, River 2 Renal Corp., Stimuliver, Guidepoint, and ICON plc, has received speaker fees from HistoIndex and Resolution Therapeutics and research grant funding from GlaxoSmithKline and Genentech. Timothy J. Kendall: TJK serves as a consultant or advisory board member for Resolution Therapeutics, Clinnovate Health, HistoIndex, Fibrofind, Kynos Therapeutics, Perspectum, Concept Life Sciences, Servier Laboratories, and Jazz Pharmaceuticals, and has received speakers' fees from Servier Laboratories, Jazz Pharmaceuticals, Astrazeneca, HistoIndex, and Incyte Corporation.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44355-026-00061-3.

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