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Metabolic dysfunction associated steatotic liver disease: mechanisms, diagnosis, and management in adults

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ABSTRACT

Metabolic dysfunction associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease globally and a major cause of liver related and cardiometabolic morbidity. MASLD is defined by the presence of hepatic steatosis and at least one of five cardiometabolic features in the absence of secondary causes of liver disease and substantial alcohol consumption (>20 g/day for women and 30 g/day for men). The recent reclassification of non-alcoholic fatty liver disease to MASLD represents a paradigm shift towards recognising the central role of systemic metabolic dysfunction and cardiometabolic risk factors in the pathogenesis of the disease and development of complications. The pathophysiology of MASLD is complex, multifaceted, and interconnected, involving adipose tissue dysfunction, altered hepatic lipid metabolism, mitochondrial and endoplasmic reticulum stress, dysregulation of the gut-liver axis, and genetic predisposition. The severity of liver fibrosis remains the strongest predictor of all cause mortality and liver specific morbidity and mortality, and the burden of cardiometabolic dysfunction affects the risk of complications in MASLD. Non-invasive serum based and imaging based biomarkers are crucial in identifying advanced liver fibrosis and guiding risk stratification. This narrative review summarises the current understanding of the pathogenesis of MASLD, the clinical use of non-invasive diagnostics, and compares international guidelines for disease management. This review also discusses approved and emerging treatment options for MASLD, recognising the current need for developing strategies for monitoring the efficacy of treatment.

Introduction

Metabolic dysfunction associated steatotic liver disease (MASLD), the new name for non-alcoholic fatty liver disease (NAFLD), has had a number of official and unofficial name changes in the past few years. Finally, in June 2023, a consensus process led by the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asociación Latinoamericana para el Estudio del Hígado established the new officially recognised nomenclature for MASLD.[1]

Under this revised disease framework, steatotic liver disease was introduced as the overarching term referring to all liver diseases characterised by hepatic steatosis, irrespective of aetiology.[1] A diagnosis of MASLD requires the presence of hepatic steatosis, typically identified by non-invasive imaging technology, such as ultrasound, in combination with one or more common cardiometabolic risk factors after the exclusion of secondary causes of liver disease (figure 1).[1 2] A diagnosis of MASLD also allows for moderate alcohol consumption (<20 and 30 g/day for women and men, respectively)[3] to discriminate pure MASLD from metabolic dysfunction alcohol related liver disease (where the amounts of alcohol consumed are 20-50 g/day for women and 30-60 g/day for men). The introduction of the new term MASLD constitutes a substantive revision in disease classification, acknowledging the advances in understanding the systemic and multiorgan characteristics of the disease, and moving beyond a liver specific perspective. Evidence indicates an almost complete overlap between populations who previously had a diagnosis of NAFLD and those now with a diagnosis of MASLD.[4–6] This finding highlights the clinical relevance of the MASLD definition and indicates that the revised criteria refine diagnostic precision without increasing the patient population.

The global prevalence of MASLD in the general adult population has increased from 25% (1990-2015)[7] to 38% (2016-19)[8] and is continuing to grow, with an expected global prevalence of 55% by 2040.[7–11] Worldwide, MASLD has become the most common chronic liver disease, and about 4-5% of adults develop MASLD each year.[8 12 13] Regional prevalences of MASLD vary greatly because of lifestyle and genetic differences,[14 15] with higher rates in Latin America (44%)[16] and lower rates in western Europe (25%).[8] Also, individuals with obesity or type 2 diabetes mellitus are disproportionately affected by MASLD,[15 17 18] with about 65-75% of this high risk population being affected by the disease.[16]

With MASLD accepted as the new nomenclature for NAFLD, a review of the mechanisms, diagnosis, and management of this common and burdensome liver disease is timely. This narrative review discusses the complex pathophysiological mechanisms of MASLD, and the use of non-invasive serum based and imaging based biomarkers used in clinical practice to identify advanced liver fibrosis. We also discuss international guidelines for identifying, managing, and monitoring MASLD in adults, as well as current and emerging drug treatment options for MASLD. Finally, we highlight current knowledge gaps in MASLD research.

Sources and selection criteria

Clinical pharmaceutical trials in MASLD or metabolic dysfunction associated steatohepatitis (MASH) were identified on 31 August 2025 from ClinicalTrials.gov with the search terms: "non-alcoholic fatty liver disease" OR "NAFLD" OR "non-alcoholic steatohepatitis" OR "NASH" OR "metabolic dysfunction-associated steatotic liver disease" OR "MASLD" OR "metabolic dysfunction-associated steatohepatitis" OR "MASH". Filters applied were: not yet recruiting, recruiting, active (not recruiting); phase: 3; study type: interventional.

Non-invasive serum based and imaging based biomarkers for liver fibrosis were identified on 31 August 2025 from PubMed with the search criteria: "metabolic dysfunction-associated steatotic liver disease" OR "MASLD" OR "non-alcoholic fatty liver disease" OR "NAFLD" AND "Enhanced Liver Fibrosis test" OR "ELF test" OR "FIB-4" OR "AST to ALT ratio" OR "BARD score" OR "NAFLD fibrosis score" OR "APRI score" or "FibroScan" OR "vibration-controlled transient elastography" OR "VCTE" or "magnetic resonance imaging" OR "MRE" OR "point shear wave elastography" OR "pSWE". Filters applied were: meta-analysis, date: 2020-25, free full text, humans, adults aged ≥19 years. We only considered articles in peer reviewed journals.

Prognosis and complications

The severity of liver fibrosis remains the strongest predictor of all cause mortality and liver specific morbidity and mortality in people with MASLD.[19–23] Based on the histology results of liver biopsy, the severity of liver fibrosis is scored on a five stage scale: F0 (absence of fibrosis), F1 (perisinusoidal or portal fibrosis), F2 (perisinusoidal and portal or periportal fibrosis), F3 (septal and bridging fibrosis), and F4 (cirrhosis). The risks of all cause and liver specific mortality and morbidity increase with advancing severity of fibrosis (figure 1).[19–22 24–27] Worldwide, MASLD has rapidly become the most common chronic liver disease[10] and represents a major research priority because of its rising global prevalence and substantial clinical burden.

MASLD is a key risk factor for hepatocellular carcinoma. The risk of hepatocellular carcinoma increases in parallel with the severity of liver fibrosis and is highest in those with cirrhosis, where the annual incidence of hepatocellular carcinoma is thought to be about 0.7-2.5%.[28 29] MASLD also increases the risk of fatal and non-fatal cardiovascular disease events,[30] chronic kidney disease stage ≥3,[31] and some extrahepatic cancers (eg, gastrointestinal, urinary tract, and breast cancers),[32 33] and impairs quality of life.[34 35] Confirming its multisystem nature, the cardiac specific, extrahepatic cancer specific, and liver specific mortality rates

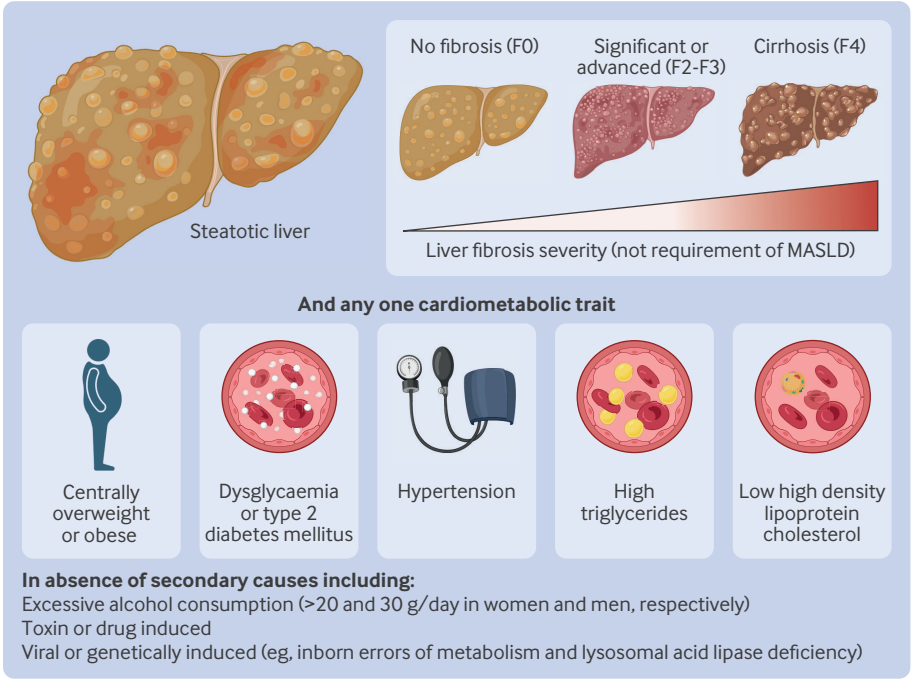

Figure 1 | Diagnosis of metabolic dysfunction associated steatotic liver disease (MASLD). Diagnosis of MASLD requires evidence of hepatic steatosis in combination with one of five common cardiometabolic features after excluding the presence of substantial alcohol consumption and other secondary causes of liver disease. Although not a requirement of MASLD, liver fibrosis is a crucial clinical characteristic of the severity of MASLD and spans from no fibrosis (F0), to mild fibrosis (F1), significant fibrosis (F2), advanced fibrosis (F3), and cirrhosis (F4). Created with BioRender.com

are thought to account for about 33%, 23%, and 7%, respectively, of total mortality in patients with MASLD.[9]

Pathophysiology

Figure 2 illustrates a framework for understanding how disruptions in adipose tissue function, lipid metabolism, inflammatory signalling, gut-liver axis crosstalk, and genetic predisposition may interact to drive hepatic steatosis, systemic cardiometabolic dysfunction, and ultimately progression to liver fibrosis and advanced chronic disease states. Although this review provides an overview of key pathophysiological mechanisms underlying MASLD, a comprehensive discussion is available in the recent literature.[36–38]

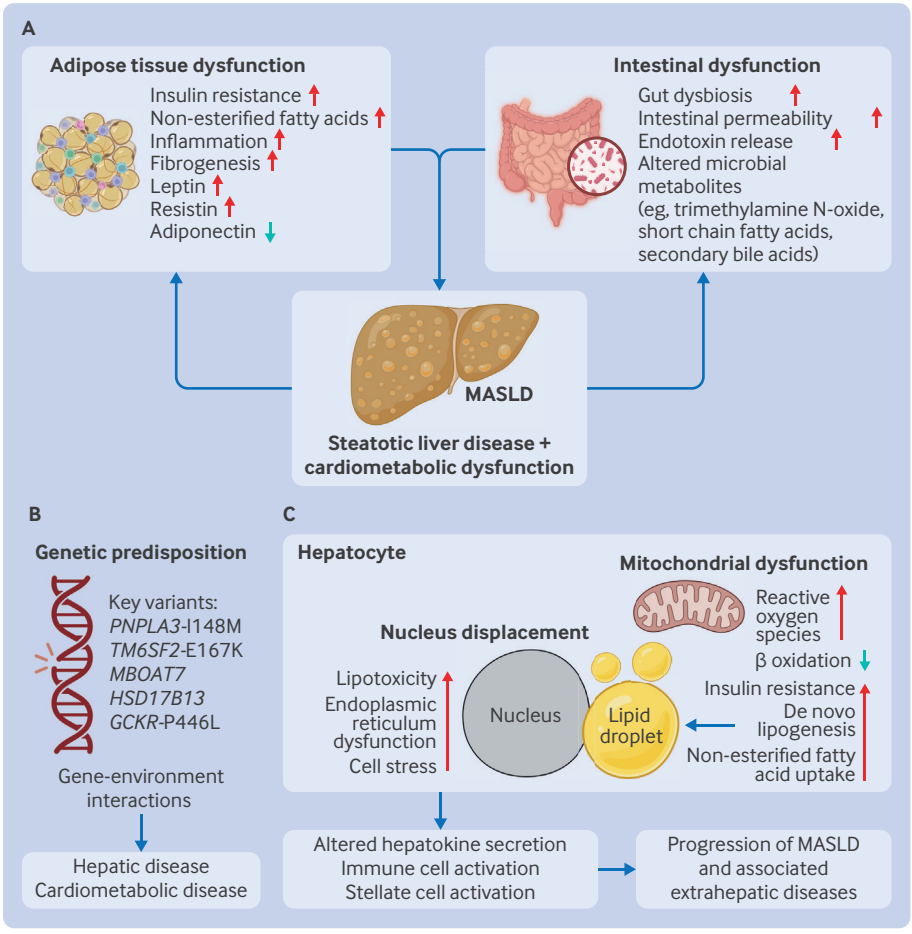

Figure 2 | Overview of the key factors in the pathogenesis of metabolic dysfunction associated steatotic liver disease (MASLD). (A) Dysfunctional adipose tissue characterised by increased insulin resistance, inflammation, fibrogenesis, and a shift in the production of adipokines is strongly associated with MASLD. Collectively, these changes can increase the flux of non-esterified fatty acids to the liver, promoting hepatic steatosis and exacerbating systemic low grade inflammation and cardiometabolic dysfunction. Simultaneously, intestinal dysfunction, driven by gut dysbiosis and loss of intestinal barrier integrity, results in increased endotoxin release and changes in the production of microbial metabolites, such as trimethylamine N-oxide, short chain fatty acids, and secondary bile acids, all of which have been shown to have a role in the development and progression of MASLD. (B) Common genetic risk variants, such as *PNPLA3*-I148M, *TM6SF2*-E167K, and other variants, increase the risk of developing both MASLD and metabolic dysfunction associated steatohepatitis (MASH) and its extrahepatic complications through a wide range of mechanisms. Crucially, the presence of these genetic variants alone is insufficient to cause MASLD; gene-environment interactions with overall adiposity, metabolic dysfunction, and diet are critical determinants of the disease phenotype. Gene variants are: *PNPLA3*=patatin-like phospholipase domain containing protein 3; *TM6SF2*=transmembrane 6 superfamily member 2; *MBOAT7*=membrane bound O-acyltransferase domain containing 7; *HSD17B13*=hydroxysteroid 17-beta dehydrogenase 13; and *GCKR*=glucokinase regulatory protein. (C) Within hepatocytes, increased de novo lipogenesis, excess uptake of non-esterified fatty acids, and insulin resistance drive the accumulation of lipid droplets. Once established, hepatic lipid droplets are thought to displace the cell's nucleus, induce endoplasmic reticulum stress, and be strongly associated with the generation of lipotoxic lipid intermediates, such as ceramides and diacylglycerol. Simultaneously, mitochondrial dysfunction can promote oxidative stress and reduce fatty acid oxidation, further driving hepatic steatosis and inflammation. Collectively, these processes may induce hepatocyte dysfunction, leading to the activation of resident immune cells and stellate cells that drive the progression of MASLD to MASH, advanced fibrosis, and cirrhosis. Created with BioRender.com

Adipose tissue dysfunction and lipid metabolism

When subcutaneous adipose tissue expansion is inadequate or insulin resistance impairs the suppression of lipolysis, or both, increased flux of non-esterified fatty acids into visceral adipose tissue and the liver is seen, where these fatty acids provide a key fuel source for the formation and expansion of hepatic lipid droplets.[39] Clinical studies have shown a positive association between markers of adipose tissue insulin resistance, such as the adipose tissue insulin resistance index and adiponectin concentrations, and both the presence and progression of MASLD.[31 40 41] Excess hepatic non-esterified fatty acids also contribute to the formation of toxic lipid intermediates, such as ceramides and diacylglycerols, that are known to contribute to hepatocyte dysfunction and inflammation.

The hypertrophic expansion of adipocytes can lead to the recruitment and activation of immune cells, propagation of inflammatory signalling, and release of proinflammatory mediators, such as tumour necrosis factor α and interleukin 1β. Consequently, adipose tissue can become fibrotic, further limiting its expansion and exacerbating hepatic lipid deposition and metabolic dysfunction.[31 42] Markers of adipose fibrogenesis, such as the expression of collagen VI gene isoforms and transforming growth factor β, were found to be associated with the presence and severity of MASLD.[31 42] As adipose tissue becomes dysfunctional, its profile of secreted adipokines (eg, leptin, adiponectin, and resistin) becomes altered, adding a further level of dysfunction.[43 44]

Hepatic mechanisms

Together with the increased release of non-esterified fatty acids from expanded and dysfunctional adipose tissue, hepatic de novo lipogenesis is pathologically upregulated in individuals with cardiometabolic disorders (figure 2). In obesity, increased expression of the transcriptional regulators sterol regulatory element binding protein 1c (SREBP-1c) and carbohydrate responsive element binding protein (ChREBP), promotes the conversion of carbohydrates into non-esterified fatty acids in the liver. This increase in de novo lipogenesis fuels the synthesis of high levels of intrahepatic triglycerides and toxic lipid intermediates, which contribute to the formation of hepatic lipid droplets and inflammation.[45] The expansion of hepatic lipid droplets is also thought to induce physical stress and distort the cell nuclei, potentially exacerbating cell stress, inflammation, and hepatic fibrogenesis.[46 47] Increased dietary fructose is now recognised as a driver of hepatic lipid accumulation and inflammation in MASLD.[48 49]

Beyond local effects, changes in the secretion of hepatic signalling proteins (ie, hepatokines), such as fibroblast growth factor 21, fetuin-A, and angiopoietin-like proteins, can also have important roles in the pathophysiology of MASLD. These changes have been proposed to affect inter-organ communication and negatively affect nutrient metabolism in both the liver and extrahepatic tissues, such as muscle and adipose tissue.[43]

Gut-liver axis and microbiome dysfunction

The gut microbiota and gut-liver axis have important roles in the pathophysiology of MASLD, and intestinal dysbiosis is commonly seen in patients with MASLD (figure 2). In a randomised trial of patients with NAFLD that also monitored changes in the faecal microbiome by 16S ribosomal DNA sequencing, a symbiotic combination (probiotic and prebiotic) given for one year changed the faecal microbiome but did not reduce liver fat content or markers of liver fibrosis.[50] Recent meta-analyses indicate that the gut microbiome in patients with MASLD is typically less taxonomically rich and diverse than those of healthy individuals.[51–53] Also, MASLD is often associated with an enrichment of potentially proinflammatory genera, such as *Fusobacterium* and *Escherichia*, and a depletion of barrier protective taxa, such as Ruminococcaceae and Faecalibacterium.[51–53] These compositional shifts in gut microbes are thought to impair the integrity of the intestinal barrier. A meta-analysis in 2020 of 14 studies found that markers of intestinal permeability were raised in patients with steatotic liver disease compared with healthy controls.[54] Table 1 lists some of the mechanisms (eg, intestinal dysbiosis and altered gut microbiota metabolite production) and their consequences to

Table 1 | Mechanisms and resulting health concerns or consequences of the microbiome and gut-liver axis in the pathophysiology of metabolic dysfunction associated steatotic liver disease (MASLD)

Mechanism	Consequences
Intestinal dysbiosis	Detrimentally affects the inter-organ metabolic crosstalk between the gut and other organs, including the liver[138]
Increased intestinal permeability	Translocation of microbial products and metabolites (eg, lipopolysaccharides) into the portal circulation, which can directly link gut dysbiosis and hepatic dysfunction[139]
Increased systemic lipopolysaccharide concentrations	Activation of proinflammatory pathways by toll-like receptors, leading to low grade systemic inflammation and promoting metabolic dysfunction associated steatohepatitis[140]
Alterations in microbial metabolism	Impaired hepatic lipid and glucose metabolism[138]
Shifts in the production of gut microbiota metabolites	Increased production of trimethylamine, reduced synthesis of short chain fatty acids (eg, butyrate), altered bile acid profiles, and increased endogenous ethanol production[141]

highlight the important roles of the microbiome and the gut-liver axis in the pathophysiology of MASLD.

Genetic predisposition

Genetic predisposition accounts for about 50% of the variability in MASLD, and genome-wide association studies have identified the most common genetic determinants.[55 56] The most common and effective genetic determinant of MASLD is the patatin-like phospholipase domain containing protein 3 (*PNPLA3*) rs738409 variant, which results in an isoleucine to methionine substitution at position 148 (I148M).[57] This risk allele is thought to be present in about 25% of the global population, although studies indicate that its distribution varies between populations.[58] Table 2 summarises the functional consequences and clinical effect of *PNPLA3*-I148M. The detrimental effect of *PNPLA3*-I148M is strongly modified by overall adiposity and metabolic dysfunction through gene-environment interactions.[59–61] As well as *PNPLA3*-I148M, other genetic variants, such as transmembrane 6 superfamily member 2 (*TM6SF2*) (E167K)[62] and membrane bound O-acyltransferase domain containing 7 (*MBOAT7*) (rs641738)[62] may contribute to the development and progression of MASLD (table 2).[56] Genomic studies have highlighted the importance of genetics in MASLD and the potential use of polygenic and partitioned polygenic risk scores to identify those at risk of complications of MASLD, and to group patients with MASLD according to different risks for hepatic and extrahepatic complications.[56 63]

Diagnosis

Early detection of MASLD is challenging, mainly because the disease is asymptomatic and currently, no specific test exists for MASLD. MASLD is often discovered incidentally during routine blood tests or abdominal ultrasounds for other conditions. For example, a clinician may investigate liver health after an incidental finding of a steatotic liver on ultrasonography or after a routine liver function test that indicates abnormal levels of liver enzymes, such as an increased level of serum alanine aminotransferase. An abnormal liver function test can indicate potential problems with the liver, such as cell damage or impaired liver function,[64 65] and is useful for identifying patients at risk. A normal liver function test does not exclude MASLD, however, especially in asymptomatic patients.[66] When a problem with the liver is suspected, the approach to identifying patients with MASLD is usually sequential,[36] but must include testing for and exclusion of other causes, such as viral hepatitis, haemochromatosis, and metabolic dysfunction alcohol related liver disease or alcoholic liver disease. Alcoholic liver disease should be assessed by careful history and may be supplemented by new biomarkers, such as phosphatidylethanol, a direct biomarker for alcohol quantification,[67] which can be used together with a clinical history to objectively quantify alcohol consumption and differentiate between metabolic and alcohol related aetiologies.[68]

Non-invasive serum biomarkers

The gold standard for identifying and staging liver fibrosis is liver biopsy.[69] Liver biopsy, however, is an invasive procedure with poor patient acceptance,[70 71] is time consuming and costly, and sampling errors can occur.[72–76] Also, given the global healthcare burden of MASLD, liver biopsies do not provide a scalable approach to identifying or monitoring liver fibrosis.[8 12 13] Non-invasive serum biomarkers can be a potential alternative and replacement for liver biopsy.[77] These biomarkers are reproducible, avoid sampling errors, and eliminate intraobserver variations.[72 78] Initially, serum biomarkers for liver fibrosis were developed by secondary care physicians to detect patients with advanced liver fibrosis (≥F3). In liver fibrosis staging, both direct and indirect biomarkers are used.[79] Indirect biomarkers are routine serum based laboratory tests, such as levels of serum alanine aminotransferase and aspartate aminotransferase.[79] Alanine aminotransferase is produced in the cytosol, and although not specific to the liver, aspartate aminotransferase produced

Table 2 | Examples of key genetic variants related to metabolic dysfunction associated steatotic liver disease (MASLD)

Variant	Gene	Genetic effect	Functional consequence	Clinical effect
rs738409 (I148M)	*PNPLA3*	Isoleucine to methionine substitution at position 148[57]	Impaired triglyceride hydrolase activity, protein accumulation on hepatic lipid droplets, impaired degradation, and dominant negative effect on other lipases[142–144]	Strong association with progressive MASLD forms, including hepatocellular carcinoma, with an odds ratio of 1.5-3.0 per risk allele.[57 58 145] Effect is influenced by gene-environment interactions, such as adiposity[57–59 146]
E167K	*TM6SF2*	Loss of function[62]	Impairs very low density lipoprotein secretion[62]	Promotes hepatic fat accumulation but paradoxically lowers concentrations of low density lipoprotein cholesterol[2]
rs641738	*MBOAT7*	Variant not explicitly detailed as loss of function[62]	Affects phospholipid remodelling[62]	Promotes hepatic inflammation and fibrosis[62]

MBOAT7, membrane bound O-acyltransferase domain containing 7; *PNPLA3*, patatin-like phospholipase domain containing protein 3; *TM6SF2*, transmembrane 6 superfamily member 2.

in the liver is generated in mitochondria. These markers reflect changes in hepatic function and are widely used in clinical practice as indicators of liver injury.[80] Neither enzyme, however, is particularly valuable for assessing liver fibrosis.[79] Conversely, direct biomarkers, such as circulating levels of hyaluronic acid and procollagen III N terminal peptide, and tissue inhibitor of matrix metalloproteinase 1, are associated with the pathogenesis of liver fibrosis at the molecular and cellular levels.[81]

Several non-invasive serum biomarkers are validated against liver biopsy, including the aspartate aminotransferase to alanine aminotransferase ratio, aspartate aminotransferase to platelet ratio index, BARD (body mass index, aspartate aminotransferase, alanine transaminase, and diabetes status) score, fibrosis 4 index, and NAFLD fibrosis score (figure 3 and table 3). These five non-invasive biomarkers use a combination of direct markers and routine patient data (eg, age, body mass index, and diabetes status). These non-invasive biomarkers are available to use in both primary and secondary care and can exclude liver fibrosis stage ≥F3 in varying degrees.[77] The enhanced liver fibrosis test, also available in primary and secondary care, uses serum concentrations of hyaluronic acid, procollagen III N-terminal peptide, and tissue inhibitor of matrix metalloproteinase 1 to assess advanced liver fibrosis. Table 3 shows the overall performance of these biomarkers in identifying liver fibrosis stage ≥F3 when used in isolation.

Among these biomarkers, fibrosis 4 and NAFLD fibrosis scores are the highest performing, with values for area under the receiver operating characteristic curve of 0.81 (95% confidence interval (CI) 0.77 to 0.84) and 0.82 (0.78 to 0.85), respectively.[82] The sensitivity of these scores is relatively poor, however, at 0.57 (95% CI 0.39 to 0.74) and 0.30 (0.27 to 0.33), respectively,[82] meaning that people with definite disease can be missed. Conversely, the specificity of fibrosis 4 and NAFLD fibrosis scores is high at 0.89 (95% CI 0.77 to 0.95) and 0.96 (0.95 to 0.96), respectively,[82] indicating the effectiveness of these biomarkers in correctly identifying patients without fibrosis stage ≥F3. Overall, the enhanced liver fibrosis test shows the highest sensitivity and specificity at 0.71 (95% CI 0.58 to 0.80) and 0.76 (0.65 to 0.85), respectively,[83] making it a reliable test for both detecting and ruling out ≥F3 fibrosis. Figure 3 summarises the serum biomarkers currently recommended for use in clinical practice, along with their cut-off values for identifying ≥F3 fibrosis.

Several less widely available non-invasive serum biomarkers have been validated against liver biopsy, such as NIS2+ (micro ribonucleic acid-34a-5p, chitinase 3-like protein 1 (also known as YKL-40), and sex),[84] MACK-3 (aspartate aminotransferase, homeostasis model assessment insulin resistance, and cytokeratin-19),[85] and ADAPT (age, diabetes status, N terminal propeptide of type III collagen, and platelet count) scores.[86] NIS2+, MACK-3, and ADAPT scores performed strongly in detecting MASH, with values for area under the receiver operating characteristic curve of 0.81 (95% CI 0.80 to 0.83),[84] 0.80 (0.77 to 0.81),[87] and 0.86 (0.79 to 0.91),[87] respectively. These biomarkers, however, have one or more components in their algorithm that are proprietary or require specialist equipment or technical skills, or both, making them expensive and therefore not widely available in clinical practice.

Imaging based biomarkers

Serum biomarkers are mainly used to group patients with MASLD according to the likelihood of advanced liver fibrosis (≥F3). The use of serum biomarkers is limited, however, because additional confirmatory tests are required to accurately determine the fibrosis stage. Relying only on a non-invasive serum biomarker without further confirmation can result in misdiagnosis.[88] Therefore, imaging methods, such as vibration controlled transient elastography, magnetic resonance elastography, and point shear wave elastography, are used to confirm the stage of liver fibrosis by measuring the physical stiffness of liver tissue and providing a liver stiffness measurement (table 3 and figure 3). Vibration controlled transient elastography and point shear wave elastography use ultrasound based technology to propagate a shear wave through the skin and into the liver. Vibration controlled transient elastography machines are available as portable and fixed devices, are used in both primary and secondary care settings, and offer good overall performance for identifying liver fibrosis ≥F3, with an area under the receiver operating characteristic curve of 0.90 (95% CI 0.87 to 0.92).[89] Point shear wave elastography performs better than vibration controlled transient elastography for identifying liver fibrosis ≥F3, with an area under the receiver operating characteristic curve of 0.94 (95% CI 0.91 to 0.96).[89] Point shear wave elastography is only available in secondary care, however, as the device is not currently portable. Magnetic resonance elastography is also a fixed device and is only available in a secondary care setting. This imaging technique combines magnetic resonance imaging with low frequency vibration to produce an elastogram, a visual map of tissue elasticity.[90] Magnetic resonance elastography performs better than vibration controlled transient elastography and point shear wave elastography in identifying liver fibrosis ≥F3, with

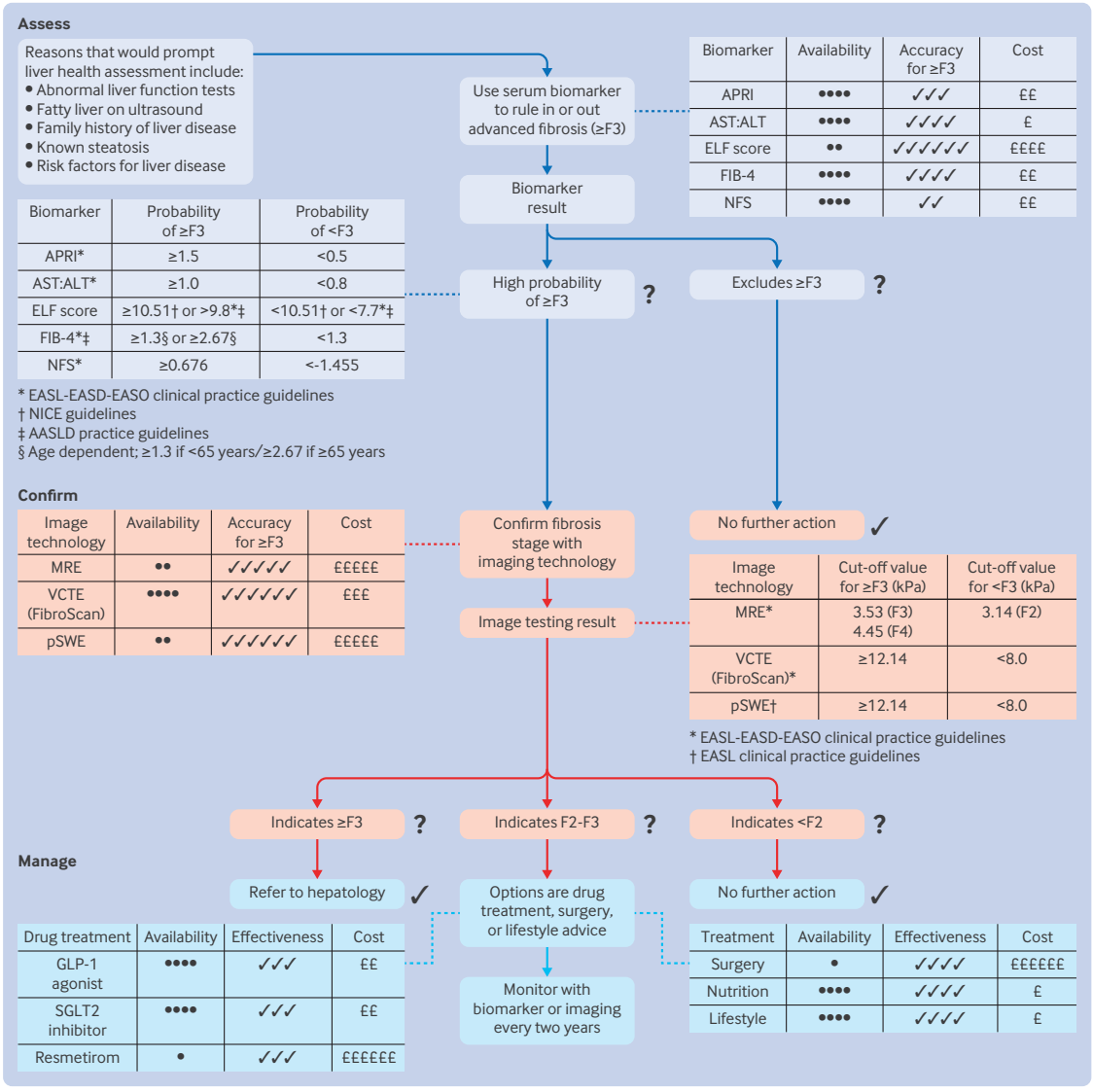

Figure 3 | Identifying advanced liver disease in patients with metabolic dysfunction associated steatotic liver disease (MASLD): summary of the processes for assessing, confirming, and managing patients. The flow begins by using a serum biomarker to identify patients at risk of liver disease. A decision on what to do next is based on the result of the serum biomarkers (cut-off values for biomarkers for clinical management are shown in the table). When the serum biomarker indicates a high probability of liver fibrosis stage ≥F3, imaging technology is used to confirm the fibrosis stage, which then informs the clinical diagnosis and management. Sources are: EASL-EASD-EASO=European Association for the Study of Liver-European Association for the Study of Diabetes-European Association for the Study of Obesity clinical practice guidelines[49]; NICE=National Institute for Care and Excellence guidelines[92]; AASLD=American Association for the Study of Liver Diseases practice guidelines[93]; and EASL Clinical Practice Guidelines.[147] Severity of fibrosis is categorised as significant fibrosis (F2), significant to advanced liver fibrosis (F2-F3), advanced fibrosis (F3), and cirrhosis (F4). APRI=aspartate aminotransferase to platelet ratio index; AST:ALT=aspartate aminotransferase to alanine transaminase ratio; ELF=enhanced liver fibrosis; FIB-4=fibrosis 4 index; GLP-1=glucagon-like peptide 1; MRE=magnetic resonance elastography; NFS=non-alcoholic fatty liver disease fibrosis score; pSWE=shear wave elastography; SGLT2=sodium-glucose cotransporter 2; VCTE=vibration controlled transient elastography

an area under the curve of 0.94 (95% CI 0.91 to 0.95).[91]

International guidelines on diagnosing advanced fibrosis and cirrhosis

Guidelines for assessing, diagnosing, and monitoring MASLD differ across regions. The current UK guidelines from the National Institute for Care and Excellence (NICE) recommend the use of the enhanced liver fibrosis as a first line test, followed by vibration controlled transient elastography.[92] NICE currently recommends a diagnosis of liver fibrosis ≥F3 if the enhanced liver fibrosis score is ≥10.51.[92] Conversely, if the enhanced liver fibrosis score is <10.51, fibrosis ≥F3 is unlikely to be present.[92] The entry criteria for MASLD

Table 3 | Comparison of non-invasive serum based and imaging based biomarkers and optimal cut-off values for identifying advanced fibrosis in metabolic dysfunction associated steatotic liver disease (MASLD), and availability for use in primary and secondary care

Biomarker	Components	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	Performance (AUROC) (95% CI))	Advantages and disadvantages
Serum based biomarkers						
APRI score[82]	AST and platelet count	≥1 for advanced fibrosis	0.45 (0.29 to 0.62)	0.89 (0.83 to 0.93)	0.83 (0.80 to 0.86)	Uses routine blood tests, low cost, easy to calculate, better at excluding than identifying disease
AST:ALT ratio score[82]	AST and ALT	≥0.8 for advanced fibrosis	0.63 (0.44 to 0.79)	0.77 (0.68 to 0.84)	0.78 (0.74 to 0.81)	Uses routine blood tests, low cost, easy to calculate, should not be used as a standalone diagnostic test
BARD score[82]	Body mass index, AST, ALT, and diabetes status	≥2 for advanced fibrosis	0.72 (0.58 to 0.83)	0.65 (0.55 to 0.75)	0.74 (0.70 to 0.77)	Uses routine blood tests, low cost, easy to calculate, should not be used as a standalone diagnostic test
Enhanced liver fibrosis score†[83]	Hyaluronic acid, TIMP-1, and PIIINP	≥9.6 for advanced fibrosis (Youden index calculation)	0.71 (0.58 to 0.80)	0.76 (0.65 to 0.85)	0.80 (0.73 to 0.86)	Propriety test, higher costs, available for clinical use, performs well for identifying the presence or absence of advanced fibrosis
Fibrosis 4 index‡[82]	Age, AST, ALT, and platelet count	≥3.25 for advanced fibrosis	0.57 (0.39 to 0.74)	0.89 (0.77 to 0.95)	0.81 (0.77 to 0.84)	Uses routine blood tests, low cost, easy to calculate, should not be used as a standalone diagnostic test
NFS[82]	Age, body mass index, diabetes status, AST:ALT ratio, platelet count, and albumin	≥0.676 for advanced fibrosis	0.30 (0.27 to 0.33)	0.96 (0.95 to 0.96)	0.82 (0.78 to 0.85)	Uses routine blood tests, low cost, easy to calculate, better at excluding than identifying disease
NIS2+[84]	Micro-ribonucleic acid-34a-5p, YKL-40, and sex	>0.68 suggests at risk NASH	0.62 (0.59 to 0.65)	0.85 (0.83 to 0.87)	0.74 (0.72 to 0.76)	Proprietary test, requires complex laboratory equipment and high technical skills, high cost
MACK-3[87]	Aspartate aminotransferase, HOMA-IR, and cytokeratin 18	>0.53 for MASH and clinically significant fibrosis	0.41 (0.34 to 0.48)	0.89 (0.85 to 0.92)	0.74 (0.70 to 0.73)	Proprietary test, high cost, mainly used in research settings
ADAPT[87]	Age, diabetes status, PRO-C3, and platelet count	>6.91 for MASH and clinically significant fibrosis	0.47 (0.39 to 0.55)	0.88 (0.83 to 0.91)	0.77 (0.73 to 0.81)	Cost of PRO-C3, currently only available as a research test, not approved for diagnostic use
Imaging based biomarkers						
FibroScan (VCTE)§[89]	Liver stiffness measurement	7.1-7.9 kPa for advanced fibrosis	0.89 (0.85 to 0.91)	0.67 (0.59 to 0.74)	0.90 (0.87 to 0.92)	Available in primary and secondary care. Easy to use but operator dependent, and provides instant results. Accuracy can be affected by body mass index or the presence of ascites. Less expensive than magnetic resonance elastography or point shear wave elastography
Magnetic resonance elastography[89]	Liver stiffness measurement	3.62-3.8 kPa for advanced fibrosis	0.88 (0.81 to 0.93)	0.91 (0.86 to 0.94)	0.94 (0.91 to 0.96)	Only available in secondary care, large sampling volume, which can accommodate patients with obesity or those with ascites, provides a three dimensional view of the liver. High cost
Point shear wave elastography[91]	Liver stiffness measurement	1.36-1.77 m/s for advanced fibrosis	0.89 (0.73 to 0.96)	0.88 (0.82 to 0.92)	0.94 (0.91 to 0.95)	Only available in secondary care, real time visualisation of the liver is offered. Lower cost than magnetic resonance elastography but higher cost than VCTE

*At risk NASH is defined as NASH with NAS ≥4 and liver fibrosis stage ≥F2.

†Recommended test in UK NICE guidelines.

‡Recommended test in EASL and AASLD guidelines.

§Recommended test in EASL, AASLD, and UK NICE guidelines.

AASLD, American Association for the Study of Liver Diseases; ALT, alanine transaminase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; EASL, European Association for the Study of Liver; HOMA-IR, homeostasis model assessment for insulin resistance; MASH, metabolic dysfunction associated steatohepatitis; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; NFS, non-alcoholic fatty liver disease fibrosis score; NICE, National Institute of Care and Excellence; PIIINP, procollagen III N terminal peptide; PRO-C3, N terminal propeptide of type III collagen; TIMP-1, tissue inhibitor of matrix metalloproteinases 1; VCTE, vibration controlled transient elastography.

assessment in the NICE guidelines are individuals in higher risk groups, such as those with type 2 diabetes mellitus or metabolic syndrome.[92] Guidelines from both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend testing all metabolically unwell populations.[49 93] Guidelines from the American Association for the Study of Liver Diseases advise using the fibrosis 4 index, followed by vibration controlled transient elastography, if the fibrosis 4 index is 1.3-2.67.[93] If the fibrosis 4 index is ≥2.67, referral to a hepatologist is recommended.[93] Similarly, guidelines from the European Association for the Study of the Liver also recommend the fibrosis 4 index as the first line test.[49] If the fibrosis 4 index is 1.3-2.67, vibration controlled transient elastography, magnetic resonance elastography, shear wave elastography, or the enhanced liver fibrosis test are suggested as alternative tests to confirm the stage of fibrosis.[49] If liver stiffness, measured by vibration controlled transient elastography, is ≥8.0 kPa or the fibrosis 4 index is ≥2.67, the European Association for the Study of the Liver recommends referral to a hepatologist[49] (figure 4). Arguably, the enhanced liver fibrosis test is superior to the fibrosis 4 index (table 3), but requires specialist laboratory analysis, which makes the enhanced liver fibrosis cost costly. The fibrosis 4 index, however, can be calculated with routine data, making it inexpensive and accessible to all healthcare practitioners.

Identifying clinically significant liver fibrosis in metabolic dysfunction associated steatotic liver disease

International guidelines do not give clear instructions on how to identify significant liver fibrosis (stage F2). Individuals with MASLD and fibrosis stage F2, however, are at increased risk of developing type 2 diabetes mellitus, cirrhosis, extrahepatic complications, including cardiovascular disease, and overall mortality,[94 95] and new treatments are licensed for stage F2 liver fibrosis (as well as stage F3 liver fibrosis; see section on treatment). Evidence indicates that about 20% of patients with a diagnosis of mild to significant fibrosis (F1-F2) will progress to advanced fibrosis or cirrhosis (F3 or F4) within five years,[96] substantially increasing their risk of death from end stage liver disease and hepatocellular carcinoma. Patients with MASLD and stages F2 and F3 are now eligible for antifibrotic treatments in some countries, which are licensed for these indications. Early detection of fibrosis stage F2 is key to preventing, controlling, treating, and managing the progression of disease, because earlier stages of liver disease can be managed with therapeutic interventions.[96–98] Currently, no global guidelines for the detection of fibrosis stage ≥F2 exist, and no one non-invasive blood biomarker is recommended for this purpose. A 2023 meta-analysis of the enhanced liver fibrosis test indicated that the optimal calculated cut-off value for detecting stage F2 fibrosis in all causes of liver disease was 9.5, with an area under the receiver operating characteristic curve of 0.81 (95% CI 0.74 to 0.87), and sensitivity was 0.73 (0.62 to 0.81) and specificity was 0.76 (0.67 to 0.83), suggesting that the enhanced liver fibrosis test may also be useful in detecting stage F2 fibrosis.[83] Further research is needed in this area, however, particularly on combining the enhanced liver fibrosis test with a second line non-invasive test.

Future directions

Machine learning has the potential to improve the precision of identifying liver fibrosis stage F2. Machine learning refers to computational methods in which algorithms are trained on sample data to identify patterns and make predictions.[99] Unsupervised machine learning models analyse unlabelled data

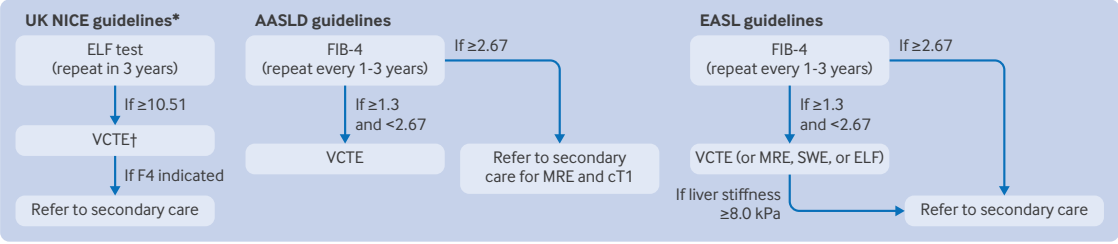

Figure 4 | Summary of UK, US, and European guidelines for identifying, managing, and monitoring liver fibrosis in metabolic dysfunction associated steatotic liver disease (MASLD). The current entry criteria for MASLD assessment in the UK National Institute for Care and Excellence (NICE) guidelines are populations at high risk, such as individuals with type 2 diabetes mellitus or those with metabolic syndrome. The entry criteria in the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of Liver (EASL) guidelines are to test all metabolically unwell populations with the fibrosis 4 (FIB-4) index. Vibration controlled transient elastography (VCTE) is the recommended second stage diagnosis method in all three guidelines. cT1=iron corrected T1; ELF=enhanced liver fibrosis; MRE=magnetic resonance imaging; SWE=shear wave elastography; F4=liver cirrhosis. *UK NICE MASLD 2026 guidelines are currently in development (https://www.nice.org.uk/guidance/indevelopment/gid-ng10434). †VCTE was recommended in 2023 as a second-stage diagnosis method in the NICE Health Tech Guidance (https://www.nice.org.uk/guidance/htg682/chapter/1-Recommendations)

to uncover patterns and iteratively learn from themselves,[99] whereas supervised machine learning models use data (eg, patient characteristics and clinical outcomes) to predict specific outcomes, such as fibrosis stage.[99] In healthcare, supervised machine learning is predominantly used for predictive modelling[100] and has been used to identify individuals at risk of fibrosis stage ≥F2. In a recently published meta-analysis, the pooled area under the receiver operating characteristic curve for the diagnostic performance of different machine learning models for identifying fibrosis stage ≥F2 was 0.83 (95% CI 0.79 to 0.86).[101] This finding suggests that machine learning based approaches may provide more accurate risk stratification for fibrosis stage ≥F2 than widely used clinical biomarkers of liver fibrosis, such as the enhanced liver fibrosis test, BARD score, aspartate aminotransferase to alanine aminotransferase ratio, fibrosis 4 index, and NAFLD fibrosis score, which are currently validated only for stage ≥F3 fibrosis.

Monitoring liver fibrosis in patients with metabolic dysfunction associated steatotic liver disease

Currently, no one non-invasive biomarker has been sufficiently validated for reliably monitoring liver fibrosis at the individual level. Monitoring changes in liver fibrosis is essential for understanding if the treatment (eg, lifestyle modifications or drug treatment interventions) provided is working. Whether non-invasive serum and imaging based biomarkers can reliably track these changes in liver fibrosis remains uncertain.[77 102 103] Currently, serum biomarkers are only validated for stage ≥F3 fibrosis. Therefore, repeating these biomarkers and using the result for prognosis requires independent validation of changes in biomarker scores against liver biopsy. Drug trials use non-invasive measures to monitor treatment responses together with liver biopsy. The ongoing phase 3 placebo controlled ESSENCE (Effect of Semaglutide in Subjects with Non-cirrhotic Non-alcoholic Steatohepatitis, NCT04822181) trial is a large international study (n=1205), whereby researchers are investigating the use of subcutaneous semaglutide 2.4 mg/week for the treatment of adults with non-cirrhotic MASH and moderate-to-advanced fibrosis.[104] At week 72, the semaglutide group had a mean improvement of 0.6 units in the enhanced liver fibrosis test, a 40% decrease in levels of serum alanine aminotransferase and γ glutamyl transferase, and a 30% decrease in serum levels of aspartate aminotransferase compared with placebo. Although these changes in non-invasive measures are encouraging, these findings apply to the whole group of participants randomised to receive semaglutide, rather than distinguishing between responders and non-responders based on the results of liver biopsy. Nevertheless, this information is encouraging and highlights the need to investigate delta responses in non-invasive markers in responders versus non-responders.

Guidelines from the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommend repeating the fibrosis 4 index test every 1-3 years to monitor liver fibrosis,[49 105] but evidence on the effectiveness of the fibrosis 4 index for monitoring the progression of the disease is conflicting. A large retrospective cohort study (n=202 319) of patients with MASLD calculated the fibrosis 4 index longitudinally. At baseline, 75%, 21%, and 4% of patients with MASLD had low, intermediate, and high fibrosis 4 index scores, respectively.[106 107] At the three year follow-up, 21% of low risk patients (fibrosis 4 index <1.45) progressed to moderate or high risk categories, whereas 55% of high risk patients (fibrosis 4 index >2.67) remained in the high risk category.[106 107] Compared with low risk patients, those who remained in the high risk fibrosis 4 index category had a significantly higher incidence of hepatocellular carcinoma (4.56 *v* 0.05 per 1000 person years; adjusted subdistribution hazard ratio 57.7, 95% CI 24.6 to 33.2).[106 107] This study confirmed that a longitudinal increase in the fibrosis 4 index score is dose dependently associated with the risk of developing hepatocellular carcinoma and cirrhosis.[106 107] In a smaller retrospective study (n=135) of patients with MASLD with a high prevalence of stage ≥F2 fibrosis, the fibrosis 4 index, aspartate aminotransferase to platelet ratio index, and NAFLD fibrosis score were weakly associated with disease progression, with suboptimal diagnostic precision (values for area under the receiver operating characteristic curve of 0.65 (95% CI 0.53 to 0.75), 0.64 (0.52 to 0.76), and 0.56 (95% CI 0.44 to 0.68) for the fibrosis 4 index, aspartate aminotransferase to platelet ratio index, and NAFLD fibrosis score, respectively).[108]

The UK NICE guidelines recommend repeating the enhanced liver fibrosis test every three years to monitor the progression of disease.[92] In a retrospective and prospective study (n=300) with paired enhanced liver fibrosis score and liver biopsies, the enhanced liver fibrosis test efficiently identified progression of liver disease in patients without stage ≥F3 fibrosis.[109] Among patients with a liver biopsy score of F0-F2 (no liver scarring to mild liver scarring), 55% with an enhanced liver fibrosis score of ≥9.8 developed clear evidence of fibrosis stage ≥F3 within an average of six years.[109] In contrast, only 3.5% of patients with stage F0-2 and an enhanced liver fibrosis score of <9.8 developed advanced disease, but over a much longer period (14.2 years).[109] Cox proportional hazards modelling indicated that each unit increase in the enhanced liver fibrosis

test significantly increased the hazard of progression to fibrosis stage ≥F3 by 4.34 times (95% CI 2.4 to 7.8), adjusted for age.

Treatment

Interventions for MASLD aim not only to achieve improvements in hepatic histology but also to provide extrahepatic benefits, particularly for cardiovascular and systemic metabolic health. This evolving therapeutic landscape includes established lifestyle interventions, nutritional supplements, bariatric surgical procedures (in selected patients with coexisting severe obesity), approved drug treatments, and an increasing number of new drugs in the pipeline targeting key pathogenic pathways (table 4). In this section, we discuss the spectrum of interventions aimed at improving liver histology, mitigating metabolic risk factors, and looking at the cardiometabolic complications of MASLD.

Lifestyle and nutritional strategies

According to the 2024 guidelines from the European Association for the Study of the Liver,[49] behavioural modifications are the first line treatment for MASLD. Lifestyle and dietary strategies trialled in patients with MASLD so far have included exercise interventions, dietary pattern recommendations aimed at inducing weight loss or modifying intakes of particular food groups, and supplementation studies of micronutrients and functional foods targeting the gut microbiome.[110] When applying lifestyle or nutritional advice, consideration should also be given to screening for disordered eating behaviours, given that a substantial prevalence of binge eating disorder exists in patients with MASLD, estimated to be >20%.[111–113]

Fewer than half of the behavioural interventions that aim to promote weight loss in patients with MASLD achieve their objective, but predictors of success include designs with frequent in-person interventions and clear guidance on recommendations for both physical activity and dietary intakes.[114] The benefits of exercise interventions are independent of weight loss, with an estimated mean reduction of 24% in liver fat measured by magnetic resonance imaging; the greatest impact was seen with interventions equivalent to at least 150 min of brisk walking/week.[115] When Mediterranean dietary patterns are recommended, systematic reviews have highlighted beneficial changes in metabolic markers and liver function tests despite modest changes in body composition.[116] Conversely, diets with a higher proportion of ultra processed foods have been linked to MASLD in cross sectional, case-control, and prospective study designs.[117] These observations align with public health messages on dietary recommendations and physical activity.

Approved drug treatment interventions

Resmetirom

Resmetirom, an oral thyroid hormone receptor β selective agonist, became the first drug to receive conditional approval from both the US Food and Drug Administration (FDA) in March 2024[118] and the European Medicines Agency in August 2025.[119] Resmetirom is currently approved for the treatment of adults when a diagnosis of non-cirrhotic MASH and moderate to advanced (F2-F3) liver fibrosis has been established, either through liver biopsy or with validated non-invasive tests. Resmetirom functions by specifically activating thyroid hormone receptor β, which is highly expressed in the liver and has a key role in regulating hepatic lipid metabolism. By activating this receptor, resmetirom modulates hepatic gene expression involved in lipid metabolism, thereby increasing hepatic fat metabolism and reducing lipotoxicity.[120] The conditional approval of resmetirom followed the pivotal phase 3 placebo controlled MAESTRO-NASH (A Phase 3 Study to Evaluate the Efficacy and Safety of MGL-3196 (Resmetirom) in Patients With Non-alcoholic Steatohepatitis (NASH) and Fibrosis) of 966 patients with obesity and biopsy confirmed MASH and liver fibrosis.[121] Daily doses of 80 and 100 mg increased the proportion of patients achieving resolution of MASH without worsening of liver fibrosis (80 mg, 26%; 100 mg, 30% *v* placebo 10%) and with an improvement of ≥1 stage in liver fibrosis without worsening of MASH (80 mg, 24%; 100 mg, 26% *v* placebo 14%). In this trial, resolution of MASH was defined as a hepatocellular ballooning score of 0, lobular inflammation score of 0 or 1, and reduction in the NAFLD activity score by ≥2 points.[121] Apart from histological liver endpoints, resmetirom did not change body weight or improve insulin resistance, but significantly reduced circulating levels of low density lipoprotein cholesterol, lipoprotein(a), and triglycerides.[121]

The incidence of serious adverse events was similar across trial groups: 10.9% and 12.7% in the 80 mg and 100 mg resmetirom groups, respectively, and 11.5% in the placebo group. The incidence of non-serious adverse events was similar between treatment and placebo groups. After 52 weeks, ending the trial was more common in the 100 mg resmetirom group (6.8%) than in the 80 mg or placebo groups (1.9% and 2.2%, respectively). These findings indicate that, within this cohort, resmetirom was well tolerated, with gastrointestinal adverse events being the most frequently reported. This study also reported non-clinically significant changes in thyroid function tests without evidence of systemic thyrotoxicity. Resmetirom is contraindicated in patients with decompensated cirrhosis, and caution is advised in individuals with pre-existing thyroid disease. Also, data in elderly patients are limited. The MAESTRO-NAFLD open label extension trial (NCT04951219) is ongoing to assess the

Table 4 | Ongoing phase 3 pharmaceutical trials in adults with metabolic dysfunction associated steatotic liver disease (MASLD) or metabolic dysfunction associated steatohepatitis (MASH)

National Clinical Trial and duration	Treatment arms (route of administration)	Target population (estimated No of patients)	Primary outcomes	Status (expected completion)
NCT04951219 52 weeks	Resmetirom 80 mg/day for 12 weeks and 100 mg/day for 40 weeks Resmetirom 100 mg/day for 52 weeks (oral tablet)	Adults with biopsy proven MASH (n=1000)	Incidence of adverse events	Active, not recruiting (April 2026)
NCT04849728 part A, 72 weeks Part B, 48 weeks after completion	Lanifibranor 800 mg/day Lanifibranor 1200 mg/day Placebo (oral tablet)	Adults aged ≥18 years with biopsy proven MASH (n=1000)	Part A: resolution of MASH and improvement in fibrosis by biopsy Part B: adverse events, adjudicated liver events, drug induced liver injury, and major adverse cardiac events	Active, not recruiting (September 2026)
NCT06161571 52 weeks	Efruxifermin 50 mg/week Placebo (subcutaneous injection)	Adults aged 18 or 19-90 years with suspected or biopsy confirmed MASH or non-invasively with a diagnosis of MASLD (n=700)	Extent of use, number of participants with adverse events, severity, and clinically significant changes in clinical assessments	Active, not recruiting (October 2026)
NCT05500222 3 years	Resmetirom 80 mg/day Placebo	Adults with MASH related compensated cirrhosis (n=700)	Any incident event of all cause mortality, liver transplant, ascites, hepatic encephalopathy, gastro-oesophageal variceal haemorrhage, and confirmed increase in MELD score from <12 to ≥15 due to liver disease	Active, not recruiting (January 2027)
NCT06318169 52 weeks	Pegozafermin 44 mg/week Pegozafermin 30 mg/week Placebo (subcutaneous injection)	Adults aged18-80 years with biopsy confirmed MASH, fibrosis stage F2-F3 (n=1050)	≥1 stage improvement in fibrosis without worsening of MASH Resolution of MASH without worsening of fibrosis Time to disease progression	Active, recruiting (February 2029)
NCT04822181 4.5 years	Semaglutide 2.4 mg Placebo (subcutaneous injection)	Adults aged ≥18 years with biopsy confirmed MASH and fibrosis stage F2-F3 (n=1197)	Resolution of MASH and no worsening of liver fibrosis Improvement in liver fibrosis and no worsening of MASH Cirrhosis free survival	Active, not recruiting (April 2029)
NCT06632457 1.5-4.5 years	Survodutide (dose not specified) Placebo (subcutaneous injection)	Adults aged ≥18 years with biopsy proven MASH related compensated cirrhosis and hepatic steatosis (n=1590)	Time to first occurrence of composite endpoint: all cause mortality, liver transplant, hepatic decompensation, worsening MELD score ≥15, or progression to clinically significant portal hypertension	Active, recruiting (June 2029)
NCT06528314 96 weeks-5 years	Efruxifermin 50 mg/week Placebo (subcutaneous injection)	Adults with biopsy proven MASH related compensated cirrhosis (n=1150)	Time to first occurrence of disease progression ≥1 stage improvement in fibrosis without worsening of MASH	Active, recruiting (October 2029)
NCT06419374 2-5 years	Pegozafermin (dose not specified) Placebo (subcutaneous injection)	Adults aged 18-75 years with biopsy confirmed MASH related compensated cirrhosis (n=762)	Fibrosis regression Time to disease progression	Active, recruiting (June 2031)
NCT06632444 1-7 years	Survodutide (dose not specified) Placebo (subcutaneous injection)	Adults aged ≥18 years with biopsy proven MASH and stable body weight (n=1800)	Resolution of MASH without worsening of fibrosis ≥1 stage improvement in fibrosis without worsening of MASH Composite clinical endpoint: all cause mortality, liver transplant, hepatic decompensation, worsening MELD score ≥15, or clinically significant portal hypertension progression	Active, recruiting (December 2031)
NCT06215716 1-4.5 years	Efruxifermin 28 mg/week Efruxifermin 50 mg/week Placebo (subcutaneous injection)	Adults aged 18-80 years with biopsy proven MASH (n=1650)	Resolution of MASH with ≥1 stage improvement in fibrosis Event free survival	Active, recruiting (November 2032)

Three phase 3 clinical trials were identified but were omitted because the eligibility criteria for ongoing studies were no longer met. The MAESTRO-NASH trial of resmetirom (MGL-3196; NCT03900429) has been completed with published results and subsequent regulatory filings. The ARMOR trial of aramchol (NCT04104321) was suspended after an interim futility analysis. A planned phase 3 trial of denifanstat (NCT06692283) was withdrawn before recruitment.

MELD, model for end stage liver disease.

long term safety of resmetirom, and the MAESTRO-NASH-OUTCOMES trial (NCT05500222) is currently evaluating its efficacy in patients with MASH related compensated cirrhosis (table 4).

Semaglutide

In August 2025, subcutaneous semaglutide 2.4 mg/week, a glucagon-like peptide 1 receptor agonist, was also granted accelerated approval by the FDA for the treatment of adults with non-cirrhotic MASH and moderate to advanced fibrosis together with lifestyle modifications.[122] Although the mechanisms underlying the hepatic metabolic benefits of semaglutide are not completely understood, this drug has been shown to decrease appetite and increase satiety, improve insulin resistance, reduce hepatic de novo lipogenesis by downregulating ChREBP and SREBP-1c signalling (along with the expression of other lipid synthesising genes), and suppress the expression of proinflammatory genes.[123] This approval followed part 1 of the phase 3, placebo controlled ESSENCE trial that evaluated the efficacy of semaglutide on liver outcomes in 800 adults with obesity and with MASH and moderate to advanced (F2-F3) liver fibrosis.[104] After 72 weeks, 63% of participants treated with semaglutide (2.4 mg/week) achieved resolution of MASH without worsening of fibrosis, compared with 34% in the placebo arm. In this study, resolution of MASH was defined as an NAFLD activity score of 0 for ballooning and 0-1 for inflammation. Indeed, 37% of participants treated with semaglutide achieved ≥1 stage improvement in fibrosis without worsening of MASH, compared with 22% of those receiving placebo.[104] Adverse events were reported in 86.3% and 79.7% of patients in the semaglutide and placebo groups, respectively, and 13.4% of patients in each group reported a serious adverse event. At week 72, patients taking semaglutide had greater weight loss than those receiving placebo (−10.5% *v* −2%), and improvements in insulin resistance and plasma lipid levels. The safety profile of semaglutide in patients with MASH is consistent with its established use in obesity and type 2 diabetes mellitus. The most frequently reported adverse events are gastrointestinal and typically occur during dose escalation. Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in those with multiple endocrine neoplasia syndrome type 2. Although semaglutide is widely used in older adult patients, data in patients with advanced liver disease are limited, and the drug is currently not licensed for the treatment of patients with MASH related decompensated cirrhosis.

The ongoing part 2 of the ESSENCE trial will assess the long term efficacy of semaglutide over about 4.5 years in patients with MASH and F2-F3 liver fibrosis (table 4). Despite promising efficacy in patients with MASH, an earlier phase 2b trial of 71 adults with biopsy confirmed MASH related compensated cirrhosis found that, over 48 weeks, semaglutide 2.4 mg/week did not significantly improve liver fibrosis or achieve resolution of MASH compared with placebo.[124] As well as hepatic histology, the established cardiometabolic benefits of semaglutide, including sustained weight loss and a 20% relative reduction in the risk of major adverse cardiovascular events[125] in patients with existing cardiovascular disease and obesity, further highlight its potentially transformative role in the management of MASLD.

Pipeline treatments in late phase clinical development

Although resmetirom and semaglutide are major advances, many patients with MASH and liver fibrosis do not achieve adequate histological or clinical responses, and for patients with MASH related compensated cirrhosis, no effective treatments exist. Ongoing phase 3 controlled trials are therefore exploring drugs that target complementary pathways and may be used as alternatives or in future combination regimens (table 4).

Dual incretin receptor agonists

Dual incretin agonists, such as tirzepatide (ie, a glucagon-like peptide 1 and gastric inhibitory polypeptide agonist) and survodutide (glucagon-like peptide 1 and glucagon agonist), performed well in phase 2b randomised clinical trials. In 190 patients with obesity, with biopsy confirmed MASH and F2-F3 liver fibrosis, results from SYNERGY-NASH (A Study of Tirzepatide (LY3298176) in Participants With Non-alcoholic Steatohepatitis)[126] showed that once weekly tirzepatide given subcutaneous (5, 10, or 15 mg) over 52 weeks improved resolution of MASH (defined as no steatotic liver disease or simple steatosis without MASH and an inflammation score of 0 or 1 and a ballooning score of 0) and reduced liver fibrosis by ≥1 stage more effectively than placebo. Also, all doses of tirzepatide reduced body weight, with favourable effects on the plasma lipid profile and glycaemic control. Adverse events were reported in 92% and 83% of patients in the tirzepatide and placebo groups, respectively. Moreover, incident serious adverse events were similar in the tirzepatide (6%) and placebo (6%) groups. Despite these promising results, as of August 2025, no phase 3 tirzepatide trials are underway. Conversely, survodutide, which also showed promising efficacy in a 48 week phase 2b trial of 293 patients with obesity and biopsy proven MASH and liver fibrosis,[127] is currently being investigated in two phase 3 trials (NCT06632457 and NCT06632444; table 4). These trials are investigating the long term efficacy and safety of survodutide in nearly 1800 patients with biopsy confirmed MASH and F2-F3 liver fibrosis (NCT06632444) and 1590 patients with MASH related compensated cirrhosis (NCT06632457). Results from these phase

3 trials are expected in 2029-32 and will inform potential FDA approval.

Triple incretin receptor agonists

In a phase 2 clinical trial with 338 participants, retatrutide, a triple incretin receptor agonist (glucagon-like peptide 1, gastric inhibitory polypeptide, and glucagon agonist), effectively promoted weight loss and improved cardiometabolic markers in individuals with obesity compared with placebo.[128] Moreover, retatrutide treatment for 24 weeks markedly reduced liver fat content (measured with magnetic resonance imaging-proton fat fraction), body weight, and adiposity at all investigated doses (1, 4, 8, and 12 mg/week) in patients with MASLD, but liver fibrosis biomarkers were not improved.[129] Adverse events (predominantly gastrointestinal) during the treatment period were reported in 70% of participants in the placebo group and in 73-94% of participants in the retatrutide groups, with the highest incidence rates in the 8 and 12 mg groups. The incidence of serious adverse events was similar between the retatrutide and placebo groups. These findings highlight the potential of multi-incretin treatments to manage hepatic and systemic metabolic dysfunction, warranting more phase 2 and 3 trials to assess long term histological outcomes.

Peroxisome proliferator activated receptor agonists

As well as incretin based treatments, several drugs targeting peroxisome proliferator activated receptors and the fibroblast growth factor 21 pathway are currently in late phase clinical trials. Although pioglitazone, a peroxisome proliferator activated receptor γ agonist, showed some efficacy in resolving MASH and reducing the severity of fibrosis in a meta-analysis of phase 2 trials that collectively included 516 participants,[130] patients with MASH treated with pioglitazone 30 mg/day for 96 weeks had no significant improvement in liver fibrosis compared with placebo in the phase 3 PIVENS (Pioglitazone versus Vitamin E versus Placebo for the Treatment of Non-Diabetic Patients with Nonalcoholic Steatohepatitis) trial of 247 participants.[131] This uncertainty in efficacy highlights the need for more potent pan-peroxisome proliferator activated receptor agonists. Building on promising findings from the phase 2b NATiVE trial (A Phase 2b trial evaluating the efficacy and safety of lanifibranor in 247 patients with biopsy-proven, noncirrhotic NASH),[132] lanifibranor, a pan-peroxisome proliferator activated receptor agonist, is now under phase 3 investigations for long term efficacy and safety in a target trial of 1000 participants (NCT04849728). Part A will evaluate two doses (800 and 1200 mg/day) over 72 weeks for resolution of MASH (defined by NASH Clinical Research Network scores for ballooning of 0 and inflammation of 0 to 1) and fibrosis improvement, whereas part B will assess adverse events and cardiovascular outcomes over 48 weeks after the treatment period.

Fibroblast growth factor 21 analogues and sodium-glucose co-transporter 2 inhibitors

Similarly, fibroblast growth factor 21 analogues, including efruxifermin and pegozafermin, are being evaluated in phase 3 trials in patients with biopsy proven MASH and F2-F3 fibrosis (NCT06318169 and NCT06161571) or MASH related compensated cirrhosis (NCT06528314 and NCT06419374) (table 4) over a 1.5 year period. In the recent phase 2b SYMMETRY trial (A Study of Efruxifermin in Subjects With Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis), in 181 patients with obesity and biopsy confirmed MASH related compensated cirrhosis, treatment with efruxifermin at a weekly dose of 50 mg for 96 weeks reversed cirrhosis (defined as a reduction in liver fibrosis of ≥1 stage) without worsening of MASH in a greater percentage of patients than placebo (29% *v* 11%).[133] Although phase 3 trials have yet to be conducted, treatment with 10 mg/day of the sodium-glucose cotransporter 2 inhibitor dapagliflozin over 48 weeks resulted in greater resolution of MASH and fibrosis improvement compared with placebo in a phase 2b trial of 158 patients with biopsy proven MASH.[134]

Patatin-like phospholipase domain containing protein 3 silencing

Complementing hormonal modulation, precision medicine approaches are also emerging to target genetic determinants of MASLD. Preclinical studies indicate that silencing *PNPLA3* expression with antisense oligonucleotides can reduce MASH and liver fibrosis.[135] Building on these studies, a phase 1 clinical trial explored the tolerability and safety of AZD2693, an antisense treatment targeting *PNPLA3*-I148M, at three doses (25, 50, and 80 mg/kg/week) in 51 participants over eight weeks in participants with steatotic liver disease.[136] AZD2693 reduced the expression of *PNPLA3*, was safe and well tolerated, and seemed to reduce liver fat content in a dose dependent manner. A phase 2b trial of 220 participants with MASH and F2-3 liver fibrosis who were homozygous for the *PNPLA3*-I148M variant and aged 18-75 years is currently underway and is expected to be completed in October 2025 (NCT05809934).

In summary, the therapeutic landscape for MASLD and MASH is rapidly evolving, with emerging drug treatments offering meaningful histological and metabolic benefits. Given the multifactorial pathogenesis of MASLD and residual unmet needs, particularly in patients with advanced liver fibrosis or compensated cirrhosis, a strong rationale exists for combination strategies targeting complementary

pathways.[137] This approach is especially important given that not all patients respond equally to drug treatment interventions. Integrating these drug treatments with diet and lifestyle interventions may enhance histological improvement, slow the progression of liver fibrosis, and simultaneously manage coexisting cardiometabolic risk factors, representing a promising approach for the comprehensive management of MASLD. Further clinical trials are required to explore the effectiveness of combination treatment strategies in managing MASLD.

Conclusions

MASLD is a metabolic, heterogeneous, and multisystem disease that extends beyond the liver, with the severity of liver fibrosis, cardiometabolic dysfunction, and genetic predisposition determining liver related and extrahepatic clinical outcomes. Recent advances in non-invasive diagnostics have transformed the detection of the disease and risk stratification, allowing earlier intervention. The emergence of targeted MASLD drug treatments licensed for the treatment of F2 and F3 liver fibrosis offers new opportunities, not only to stabilise or prevent the progression of liver disease, but also to target the risk of extrahepatic diseases in treating MASLD as a multisystem disease. Current challenges remain, however, including diagnosing F2 liver fibrosis, monitoring regression (or progression) of liver fibrosis, and establishing rules for stopping potentially expensive treatments when patients do not show evidence of treatment benefit. Finally, the cost effectiveness of diagnosis, monitoring, and treatment needs to be established. Given that MASLD is a multisystem disease, assessing cost effectiveness should consider the benefits (and harms) beyond the liver as part of a holistic approach to MASLD.

QUESTIONS FOR FUTURE RESEARCH

- ⇒ What is the optimum time span for monitoring the progression of liver fibrosis?
- ⇒ How can regression or progression of fibrosis be reliably monitored at the individual level?
- ⇒ How can improvement or progression of stage ≥F2 liver fibrosis be tested for and monitored?
- ⇒ How can at risk populations for MASLD be tested cost effectively?
- ⇒ What are the long term clinical and cost effectiveness outcomes of emerging drug treatments for MASLD and the extrahepatic complications across diverse patient populations?
- ⇒ What are the mechanistic links between MASLD and extrahepatic complications?
- ⇒ How do gene-environment interactions, particularly diet, adiposity, and metabolic status, modulate disease progression and treatment response?

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PATIENT INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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