Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Position paper

AISF practice guidance on pharmacological treatment of metabolic-dysfunction associated steatotic liver disease and steatohepatitis (MASLD/MASH): A 2026 Update

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ARTICLE INFO

Article history:
Received 7 December 2025
Accepted 15 February 2026
Available online xxx

Keywords:
Steatosis
Metabolic-dysfunction associated steatotic liver disease (MASLD)
Metabolic-dysfunction associated steatohepatitis (MASH)
Resmetirom
Semaglutide
Tirzepatide

ABSTRACT

Metabolic dysfunction–associated steatotic liver disease (MASLD) has rapidly emerged as the leading cause of chronic liver disease worldwide, gradually replacing viral hepatitis in clinical and epidemiological relevance. Italian data mirror global trends, with prevalence escalating in general and high-risk populations, particularly among individuals with type 2 diabetes (T2D), obesity, and metabolic syndrome (MetS). Disease progression from steatosis to steatohepatitis (MASH) and advanced fibrosis markedly increases the risk of cirrhosis, hepatocellular carcinoma (HCC), and cardiovascular mortality. Recent regulatory frameworks from FDA and EMA have accelerated therapeutic development, with Resmetirom and Semaglutide representing the first agents to achieve histological efficacy in Phase 3 trials for patients with MASH and F2–F3 fibrosis. Building upon these advances, the AISF STEPS-MASH framework provides a structured approach for the identification, selection, and monitoring of patients eligible for therapy. This position paper outlines evidence-based recommendations for the integration of emerging pharmacological strategies into clinical practice in Italy, emphasizing both high-risk and broader metabolic populations.

1. Introduction

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has emerged as the most pressing hepatological challenge of the 21st century, representing a paradigm shift from previously predominant viral hepatitis-related liver diseases. While hepatitis B and C are now controllable through effective antiviral therapies, MASLD is showing an alarming upward trajectory and has established itself as a major public health concern with significant clinical and economic implications.

Italian epidemiological data align with global trends, revealing a concerning escalation in MASLD prevalence over the two decades. The population-based Dionysos study [1], conducted in the early 2000s in Emilia, documented a steatosis prevalence of 20-25% in the general population, with clear associations with obesity, hyperglycaemia, hyperinsulinemia, and hypertension. The subsequent ABCD study conducted in healthy volunteers [2] revealed a MASLD prevalence of 48%, representing an almost two-fold increase and suggesting a progressive nature of this epidemiological transition. The clinical significance of this shift becomes evident in high-risk populations. In Italian overweight and obese cohorts, steatosis prevalence increases in parallel with body weight: 2.6% in normal-weight individuals, 24.6% in overweight subjects, 54% in obese, and 97% in severely obese individuals [2,3] (Italian diabetic populations show alarming rates, with MASLD prevalence reaching 59.6% among 38,880 patients across 160 centres [4] and 73.6% among 800 patients at tertiary diabetes centres [5]. People with metabolic syndrome (MetS) demonstrate a steatosis prevalence of 48.8% -78.8% [6,7].

Progression from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) represents a critical transition, with 20-30% of MASLD patients developing the inflammatory and fibrotic features characteristic of MASH. This evolution doubles the risk of cirrhosis through progressive hepatic fibrosis. Italian data show a prevalence of advanced fibrosis of 2% in the general population [2], with diabetic patients showing rates between 9.9 and 13.1% [5,8]. The mortality implications of MASLD are concerning, with meta-analyses reporting overall mortality rates of 12.6 per 1,000 person-years (PY): 4.20 per 1000-PY from cardiovascular causes, 2.83 per 1000-PY from extrahepatic malignancies, and 0.92

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https://doi.org/10.1016/j.dld.2026.02.014

per 1000-PY from hepatic causes [9]. Data from the Italian Liver Cancer registry (ITALICA) reveal that hepatocellular carcinoma (HCC) associated with steatotic liver disease increased from 50.4% in early 2000s to 77.3% in late 2010s [10]. Italian liver transplantation data (2012-2022) show that MASLD-related transplants increased in both HCC cohorts (from 17.7% to 30%) and non-HCC cohorts (from 9.5% to 11.8%) [11].

Recognizing the clinical significance of the MASLD spectrum, the European Medicines Agency (EMA) and Food and Drug Administration (FDA) have established comprehensive frameworks to accelerate the development of pharmacological intervention for MASH, acknowledging a substantial unmet medical need. Both agencies have identified two primary populations for clinical trials: patients with MASH and significant/advanced fibrosis (F2-F3) – "high-risk MASH patients" – and patients with compensated MASLD-related cirrhosis. For high-risk patients, the agencies established long-term outcomes over 5 years (cirrhosis progression, hepatic decompensation, liver transplantation, and mortality) and surrogate histological endpoints at 48-72 weeks [12]. Primary surrogate endpoints include MASH resolution without fibrosis worsening and improvement of fibrosis by ≥1 point without MASH worsening, potentially enabling conditional approval [12]. For patients with compensated cirrhosis, the frameworks focus on fibrosis reduction of ≥1 point without MASH worsening, MELD score improvement, and reduction in the incidence of hepatic decompensation, mortality, and liver transplantation [12].

Pivotal MASH clinical trials reflect this regulatory focus, enrolling patients with biopsy-confirmed MASH and significant fibrosis (F2-F3), nearing the greatest risk of disease progression. Trial populations demonstrate typical MASLD demographics: predominantly middle-aged (mean 50-55 years), obese (mean BMI 32-36 kg/m²), with a high prevalence of type 2 diabetes (T2D; 60-70%), dyslipidaemia (70-80%), and arterial hypertension (60-70%). Importantly, only 60-70% of patients show elevated aminotransferases, underscoring that normal liver enzymes do not exclude significant MASH or fibrosis. The high prevalence of F3 fibrosis in Phase 3 trials (~60%) creates a severity mismatch between studied populations and the broader MASLD population, who are generally characterized by lower stages of fibrosis, a relatively lower risk of hepatic complications, but a markedly higher cardiovascular mortality compared with the general population. This group of patients with MASLD and milder liver fibrosis is often affected by T2D and/or obesity, strong risk factors for liver fibrosis progression and adverse cardiometabolic outcomes. Treatment options for this subset of patients with MASLD require coordinated and multidimensional approaches aimed at both reducing the risk of fibrosis progression and, most importantly, improving survival by decreasing cardiovascular and extrahepatic events.

The evolving MASLD/MASH pharmacotherapy landscape represents a critical juncture in hepatology, with multiple promising agents advancing through late-phase development, and some already approved for other indications. This AISF clinical guidance addresses the urgent need for evidence-based recommendations to support Italian clinicians in the optimal patient selection and management of patients eligible for emerging MASLD pharmacological interventions.

2. Treatment options in MASLD patients with significant or advanced liver fibrosis: focus on Resmetirom and Semaglutide

Resmetirom and Semaglutide are currently the only pharmacological therapies to have met both key histological endpoints in Phase 3 randomized controlled trials for patients with MASLD and significant fibrosis.

In March 2024, Resmetirom obtained FDA conditional approval for the treatment of adults with MASH and fibrosis stages F2-F3, to be used in combination with diet and physical activity. The same indication was granted by the EMA in June 2025. Resmetirom is a liver-specific thyroid hormone receptor beta (TRH-β) agonist that targets the β-subunit expressed exclusively in hepatocytes, inducing an intrahepatic "hyperthyroidism" state without significantly affecting extrahepatic thyroid hormone metabolism. The drug acts on multiple metabolic pathways, including de novo lipogenesis, fatty acid β-oxidation, mitochondrial biogenesis, and VLDL synthesis [13–15].

The MAESTRO-NASH trial, an ongoing Phase 3 randomized, double-blind, placebo-controlled study, met its histological endpoints at the predefined 52-week interim analysis [16]. Among 955 patients in the per-protocol (PP) analysis, Resmetirom 80 mg and 100 mg achieved MASH resolution in significantly higher proportions than placebo: 25.9% and 29.9% respectively, *vs.* 9.7% with placebo ($p<0.001$). Similarly, significantly higher proportions achieved fibrosis improvement by at least one stage without worsening of MASH: 24.2% and 25.9% respectively, *vs.* 14.2% with placebo ($p<0.001$). These histological improvements occurred without significant weight loss (-1.8 kg to -1.2 kg in treated arms *vs.* -0.87 kg with placebo). As a key secondary endpoint, LDL cholesterol was significantly reduced after 24 weeks compared with placebo: -12% and -16% in the 80 mg and 100 mg arms respectively, *vs.* +1% with placebo ($p<0.0001$).

Resmetirom was generally well tolerated, the most common adverse events (AEs) being mild, transient diarrhea (28-34% *vs.* 16% with placebo) and mild nausea at treatment initiation (22-19% *vs.* 13% with placebo). Serious adverse events (SAEs) occurred at similar rates across treatment arms (11.8-12.7% in treated *vs.* 11.5% with placebo). Study discontinuation due to AEs was higher in the 100 mg arm (7.7%) compared with the 80 mg and placebo arms (2.8% and 3.7%, respectively). Despite increases in T4 level (16-19%) among treated patients, no clinically relevant changes in TSH, T3, or free T3 levels were observed in those with or without baseline thyroid disease [16].

Semaglutide is a GLP-1 receptor agonist (RA) that exerts multiple effects on systemic energy metabolism. GLP-1 RAs slow gastric emptying, enhance insulin sensitivity in skeletal muscle and the pancreas, provide cardioprotective effects, and regulate appetite via the mesolimbic reward system. The main mechanism of action seems related to weight loss, improved glucose control and possibly a direct anti-inflammatory effect [17]. In the liver, GLP-1 RAs improve insulin sensitivity by reducing de novo lipogenesis and gluconeogenesis probably through indirect mechanisms [18–20]. However, recent proteomic-based pre-clinical evidence has identified a specific protein signature in patients with MASH treated with Semaglutide, associated with disease resolution and involved in the modulation of fibrosis and inflammation independently of body weight loss. In this cohort, 72 circulating proteins in patients with MASH were restored by Semaglutide to a proteomic profile resembling that of healthy individuals, thus suggesting that anti-inflammatory and anti-fibrotic effects are at least partially mediated by extrahepatic GLP-1 receptor signalling and systemic biological modifications rather than weight loss alone [21].

Semaglutide received FDA conditional approval in August 2025 for the treatment of adult patients with MASH and moderate to advanced liver fibrosis. The approval was based on data from the ESSENCE study, an ongoing Phase 3 randomized, double-blind, placebo-controlled trial evaluating one-weekly Semaglutide up to 2.4 mg in patients with MASH and F2-F3 fibrosis [22]. At the 72-week interim analysis, Semaglutide met both histological endpoints: 62.9% of treated patients achieved MASH resolution compared to 34.2% with placebo ($p<0.001$). Additionally, 36.8% of treated patients achieved fibrosis improvement without MASH worsening, compared with 22.4% placebo ($p<0.001$). Both end-

Table 1
Liver- and extrahepatic efficacy for Resmetirom and Semaglutide in Phase 3 trials.

Treatment duration	MAESTRO-NASH[16]			ESSENCE[22]	
	52 weeks			72 weeks	
Treatment arm	Resmetirom 80 mg	Resmetirom 100 mg	Placebo	Semaglutide 2.4 mg	Placebo
Improvement in liver parameters					
Histology endpoints					
NASH*	25.9%	29.9%	9.7%	62.9%	34.3%
Fibrosis**	24.2%	25.9%	14.2%	36.8%	22.4%
Fibrosis ≥2 stages	8.3%	10.1%	2.8%	NA	NA
Non-invasive tests					
MRI-PDFF	-35.4% ± 2.8	-46.6% ± 2.8	-8.7% ± 2.7%	NA	NA
VCTE	-3.7 kPa	-3.7 kPa	-0.6 kPa	-31.1%	-13.5%
CAP	-39.6 dB/m ± 4.3	-41.3 dB/m ± 4.4	-14.5 dB/m ± 4.1	-43.4 dB/m	-13.1 dB/m
ELF§	-0.3 U	-0.4 U	-0.1 U	-0.6 U	0
Biochemistry°					
AST	-22.1% ± 3.9	-28.3% ± 3.9	-2.9% ± 3.8	-44.9%	-17.1%
ALT	-26.6% ± 3.7	-33.2% ± 3.9	-6.9% ± 3.8	-52.1%	-22.2%
γGT	-25.0% ± 5.5	-31.9% ± 6.3	3.3% ± 5.2	-43.1%	-11.8%
Improvement in non-liver parameters					
Body weight (kg)	-1.2% ± 0.37	-1.8% ± 0.38	-0.87% ± 0.36	-10.5%	-2%
SBP (mmHg)	-1.9% ± 0.70	-2.1% ± 0.71	0.74% ± 0.67	-5.39 mmHg	-1.39
HbA1c	1.7% ± 0.88	1.5% ± 0.89	1.5% ± 0.85	-1.08%°°°	0°°°
LDL	-25.3% ± 2.2	-27.1% ± 2.3	-9.6% ±2.1	-6.07%	-4.11%
HDL	4.7% ± 1.4	4.6% ± 1.5	2.7% ± 1.4	2.62 mg/dl	-1.95 mg/dl
ApoB2	-25.0% ± 2.0	-26.6% ± 2.0	-6.5% ± 1.9	-6.03%	-4.11%
Triglycerides°°	-22.5% ± 4.2	-28.4% ± 4.4	-3.5% ± 4.2	-16.77 mg/dl	-0.27 mg/dl
Glucose	0.72% ± 1.8	-3.4% ± 1.9	2.2% ± 1.7	-0.62 mg/dl°°°	-0.12 mg/dl°°°

Abbreviations: ALT, alanine aminotransferase; ApoB, apolipoprotein B; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; dB/m, decibel per meter; ELF, enhanced liver fibrosis score; ESSENCE, Evaluation of Semaglutide in Subjects with NASH; γGT (GGT), gamma-glutamyl transferase; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; kPa, kilopascal; LDL, low-density lipoprotein; MAESTRO-NASH, Resmetirom Phase 3 trial in metabolic dysfunction–associated steatohepatitis; mg/dL, milligram per decilitre; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NA, not applicable; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; SBP, systolic blood pressure; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography

* NASH resolution with no worsening of fibrosis;
** Fibrosis improvement ≥1 stage without NAS worsening;
§ for Resmetirom: baseline ELF ≥9.8;
° for Resmetirom: week 48 time-point;
°° for Resmetirom: baseline Triglycerides >150 mg/dl;
°°° in patients with T2D.

points were met in 32.7% of patients in the Semaglutide arm *vs.* 16.1% in the placebo arm (mean difference, 16.5%, p<0.001).

Patients treated with Semaglutide achieved significantly greater weight loss than those receiving placebo, with a mean reduction of -8.5% (p<0.001). The systemic impact was evident across critical metabolic parameters: treated patients showed greater reduction in systolic blood pressure (mean difference -4 mmHg), glycated haemoglobin (mean difference -1.08% in diabetic patients), HOMA-IR, triglycerides, LDL cholesterol, and high-sensitivity C-reactive protein (mean difference -42.4 mg/l).

Semaglutide was generally well tolerated, with 83.5% of patients able to maintain the 2.4 mg weekly dose at 72 weeks. Adverse events occurred in 86.2% of treated patients versus 79.7% in the placebo group, with gastrointestinal events (nausea, diarrhea, constipation, vomiting) accounting for most cases. Serious adverse events occurred in 13.4% of both study arms. Premature trial discontinuation due to AEs occurred in 2.6% of treated patients versus 3.3% of placebo. The incidence of acute pancreatitis was similar between the two groups: 0.4% in the treated arm *vs.* 0.5% in the placebo arm [22].

The efficacy and safety profiles of Resmetirom and Semaglutide are reported in Table 1 and Table 2.

Pharmacological evidence in patients with compensated cirrhosis remains limited, with final results still pending. The ongoing MAESTRO NASH OUTCOMES trial will further elucidate the efficacy and safety of Resmetirom in this setting. Besides, Semaglutide has shown an acceptable safety profile in a small trial on patients with Child–Pugh A cirrhosis, despite not meeting the surrogate endpoint of fibrosis improvement [23].

3. AISF STEPS-MASH: An Italian framework for patient selection and monitoring of MASH patients eligible for pharmacologic treatment

Given the upcoming availability of pharmacological therapies for MASH with F2-F3 fibrosis, we propose the AISF STEPS-MASH framework (Figure 1), building on current clinical evidence, regulatory guidance, and real-world practice needs. This framework provides a pragmatic and structured pathway for identifying and longitudinally managing patients eligible for pharmacologic treatment of fibrotic MASH. It is designed to support hepatologists and multidisciplinary teams in standardizing patient care while remaining adaptable to the organizational and resource constraints of the Italian healthcare setting.

3.1. S – Steatosis identification

Hepatic steatosis should be identified using non-invasive tools such as ultrasound (US) or controlled attenuation parameter (CAP; ≥248 dB/m) [24]. In some patients, particularly those with advanced (F3-F4) fibrosis, steatosis may no longer be detectable – a condition referred to as "burn-out MASH". In these cases, a previous history of steatosis, documentation from a previous liver

Table 2
Safety of Resmetirom and Semaglutide in Phase 3 trials.

	MAESTRO NASH[16]			ESSENCE[22]	
Treatment duration	52 weeks			72 weeks	
Treatment arm	Resmetirom 80 mg	Resmetirom 100 mg	Placebo	Semaglutide 2,4 mg	Placebo
AEs					
Any Grade	91.9%	91.6%	92.8%	86.2%	79.7%
Mild (grade 1)	22.7%	20.4%	24.0%	NA	NA
Moderate (grade 2)	55.9%	56.7%	52.6%	NA	NA
Severe (grade 3)	13.4%	14.6%	16.2%	NA	NA
TRAEs	38.5%	14.5%	27.4%	NA*	NA*
SAE	10.9%	12.7%	11.5%	13.4	13.4
TR-SAE	0.6%	0	0.3%	NA*	NA*
MACE	0.3%	0.3%	0.3%	10.8%	10.6%
Type of AEs°					
Diarrhea	27.0%	33.4%	15.6%	26.9%	12.2%
COVID-19	21.4%	16.7%	20.6%	16.8%	18.7%
Nausea	22.0%	18.9%	12.5%	36.2%	13.2%
Arthralgia	14.9%	10.8%	12.5%	6.6%	8.1%
Back pain	10.9%	8.4%	11.8%	6.4%	4.1%
UTI	10.2%	8.4%	8.4%	5.5%	6.1%
Fatigue	10.2	8.0%	8.7%	8.9%	5.6%
Pruritus	8.1%	11.5%	6.9%	NA	NA
Vomiting	8.7%	10.8%	5.3%	18.6%	5.6%
AEs of interest					
Gallbladder-related	0.9%°°	0.9%°°	0.3%°°	2.5%	1.5%
Acute pancreatitis	NA	NA	NA	0.4%	0.5%
Malignant neoplasm	1.2%	3.4%	3.4%	1.6%	2.3%

Abbreviations: AEs, adverse events; COVID-19, coronavirus disease 2019; MACE, major adverse cardiovascular event; NA, not available; NASH, non-alcoholic steatohepatitis; Pbo, placebo; SAE, serious adverse event; TRAEs, treatment-related adverse events; TR-SAE, treatment-related serious adverse event; UTI, urinary tract infection.
° most frequently reported;
°° reported as acute gallstone-related disorders;
* only the percentage of patients who prematurely discontinued treatment is reported.

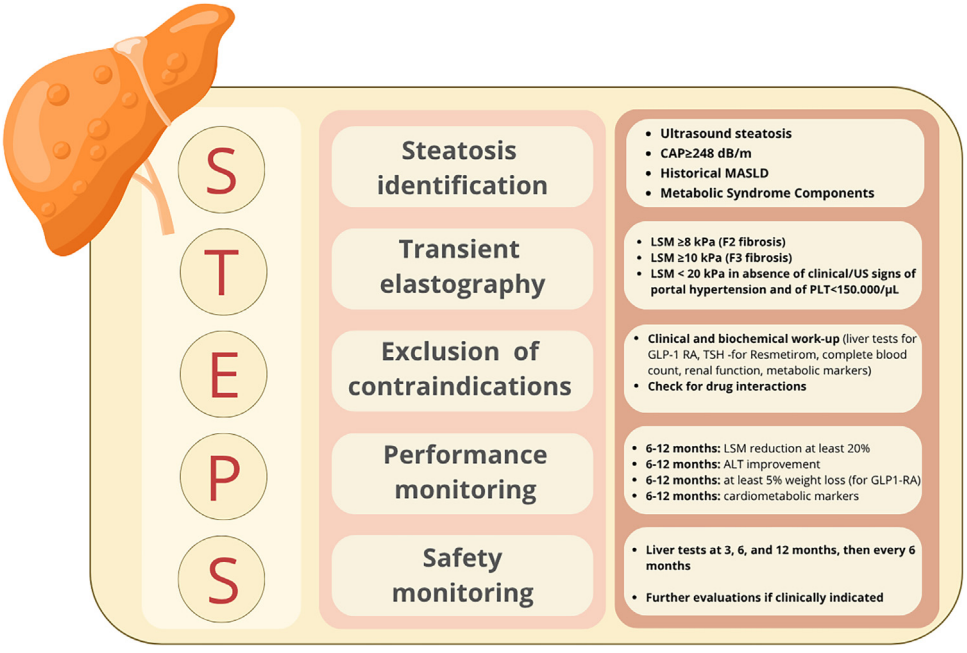

Fig. 1. The AISF-STEPS algorithm.

biopsy (LB) demonstrating steatosis, or the presence of MetS components can serve as surrogate indicators of MASLD.

3.2. T –Transient elastography: fibrosis identification

Although all pivotal MASH Phase 3 studies, (including MAESTRO and ESSENCE trials), required histological confirmation of steatohepatitis with hepatocellular ballooning and lobular inflammation (and typically NAS ≥4) together with fibrosis stage F2-F3, the current label for Resmetirom does not mandate liver biopsy for patient selection. This regulatory flexibility opens the possibility that non-invasive modalities may be used to identify MASLD/MASH patients eligible for treatment, subject to validation and future label updates (e.g. Semaglutide FDA label, EMA Resmetirom label) [24–26].

The most robust and widely available non-invasive tool for fibrosis assessment is liver stiffness measurement (LSM) via vibration-controlled transient elastography (VCTE). VCTE has demonstrated excellent diagnostic performance for detecting advanced (F3-F4) fibrosis, both in clinical trials and in in real-world cohorts. LSM values ≥8 kPa identify patients at intermediate-to-high risk of advanced fibrosis [24], whereas values ≥10 kPa are predictive of compensated advanced chronic liver disease (cACLD). In this setting, VCTE can predict 5-year liver-related event (LRE) risk with an accuracy comparable to that observed in patients with histological MASH and F2-F4 fibrosis [27]. Finally, LSM values >20 kPa raise concerns for cirrhosis and should be interpreted alongside with parameters of clinically significant portal hypertension presence, such as platelets <150,000, or clinical (varices, ascites, etc) and US signs of portal hypertension [28]. The use of enhanced Liver Fibrosis (ELF) test is currently encouraged by AASLD practice guidance to select candidates to Semaglutide (cut-off 9.2 – 10.5), and for monitoring purposes [26]. However, in Italy ELF test is not reimbursed, thus limiting its use in clinical practice.

Other non-invasive tools, including magnetic resonance elastography (MRE) [29] or two-dimensional shear wave elastography (2D-SWE) [30], as well as composite scores incorporating LSM by VCTE, CAP and biochemical tests (e.g. FAST score) [31] can also help identify (rule-in) high-risk MASH patients. However, their optimal thresholds and diagnostic cut-offs are less standardized and should be interpreted with caution across different populations and technical settings. Unfortunately, their widespread use is restricted by costs, limited standardization, and availability, outside research settings [29].

In brief MASLD/MASH patients with F2-F3 fibrosis can be non-invasively identified by LSM values ≥8 kPa, or 10 kPa but <20 kPa, provided that clinical or imaging signs of cirrhosis or portal hypertension are absent.

3.3. E – Exclusion of drug interactions and contraindications

Before initiating pharmacologic therapy for fibrotic MASLD/MASH, a comprehensive pre-treatment evaluation is essential to ensure patient safety, guide treatment selection, and support adherence. A complete clinical and biochemical work-up should include liver tests (AST/ALT/ Bilirubin, INR, albumin), complete blood count (including platelet count), renal function (eGFR), metabolic markers (glucose, HbA1c, lipids profile) and anthropometrics.

For Resmetirom [32] baseline thyroid function tests (TSH and FT4) are mandatory. While thyroid dysfunction is not a formal contraindication, untreated hypothyroidism (TSH >10 mIU/l or >7 mIU/l with symptoms) and untreated hyperthyroidism should be corrected before initiation. Dosing depends on body weight: 100 mg daily for patients ≥100 kg and 80 mg for those <100 kg. Several drug-drug interactions require attention. According to Resmetirom label, dose adjustment is required in case of concomitant administration of specific drugs. For example, whilst strong CYP2C8 inhibitors (i.e. Gemfibrozil) should not be co-administered, moderate CYP2C8 inhibitors (i.e. clopidogrel) require Resmetirom reduction to 80 mg daily (for patients ≥100 kg) or 60 mg daily (for patients <100 kg). Potential DDI has been also reported for statins, which therefore require dose reduction. Rosuvastatin and simvastatin should not be administered at dosages over 20 mg daily, whilst atorvastatin and pravastatin should not exceed 40 mg daily. OATP1B1/1B3 transporter inhibitors (i.e. cyclosporine) should be avoided.

No contraindication was reported for Resmetirom. Otherwise, for Semaglutide [33], contraindications include a personal or family history of medullary thyroid carcinoma, or multiple endocrine neoplasia type 2 (MEN-2) (Table 3).

3.4. P – Performance monitoring

Non-invasive tests (NITs) represent the most feasible approach for longitudinal assessment of treatment response. Recent evidence suggests that dynamic longitudinal reductions in LSM-VCTE of ≥20% are associated with histologic improvement and lower incidence of LRE [34], thus supporting NITs dynamics as emerging surrogate endpoints. In one study, ALT reduction from baseline was associated with histological liver improvement [35], while a 1-year improvements correlated at univariate analysis with a reduced risk

Table 3
Clinical warnings and absolute contraindication to anti-MASLD/MASH therapies.

Anti-MASLD/MASH drug	Clinical warnings	Clinical management	Absolute contraindications
Resmetirom	Moderate CYP2C8 inhibitors co-administration (i.e. clopidogrel)	Resmetirom reduction to 80 mg daily (for patients ≥100 kg) or 60 mg daily (for patients <100 kg)	Strong CYP2C8 inhibitors co-administration (i.e. gemfibrozil)
	Statins co-administration	Rosuvastatin and simvastatin should not be administered at dosages over 20 mg daily, whilst atorvastatin and pravastatin should not exceed 40 mg daily	OATP1B1/1B3 transporter inhibitors co-administration (i.e. cyclosporine)
	Increased risk of acute gallbladder disease	Promptly discontinuation if acute cholelithiasis is suspected	
Semaglutide	Increased risk of acute pancreatitis	Promptly discontinuation if acute pancreatitis is suspected and avoid rechallenge after confirmation	Personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia type 2
	Increased risk of acute gallbladder disease	Promptly discontinuation if acute cholelithiasis is suspected	-
	Risk of severe gastroparesis	Promptly discontinuation if gastroparesis is suspected	-
	Increased risk of heart rate increase	Heart rate monitoring in case of palpitations or tachycardia	-
	Hypoglycemia (including severe hypoglycemia) in case of concomitant use of insulin or insulin secretagogues	Glucose monitoring in patients on insulin or sulfonylurea and re-evaluation of anti-diabetic treatment in case of hypoglycaemia	-
	Increased risk of acute kidney injury in case of volume depletion	Renal function monitoring in patients with renal impairment reporting severe gastrointestinal reactions	-
	Increased risk of diabetic retinopathy complications	Monitoring of patients with known diabetic retinopathy	-

of hepatic decompensation in MASLD patients with LSM ≥8. Available data also suggests that lifestyle-induced weight loss of at least 5% improves liver damage in MASH, a particularly relevant finding for Semaglutide-treated patients [36].

Serological and physical NITs-used either individually or in combination - such as FIB-4, FAST, MASHResInd, LSM-VCTE, MRE, Agile 3+/4, MEFIB, and acFibroMASH [29,37–39] have also been proposed, although their clinical adoption remains limited.

Longitudinal assessment of treatment efficacy – based on ≥20% VCTE reduction, ALT improvement, and ≥5% weight loss for Semaglutide - may help classify patients after 6-12 months as responders, non-responders, or "target not achieved". Moreover, treatment discontinuation should not rely solely on single time-point assessment, and longitudinal evaluation of therapeutic strategies for MASLD/MASH should also include monitoring of the cardiometabolic response, particularly lipid and glycaemic profiles. In patients with neither improvement nor deterioration of liver parameters, treatment continuation may be considered based on several factors, including patients' risk profile and the pharmacological agent used. For Resmetirom, disease stabilization without progression may represent a clinically meaningful outcome, particularly when considering its established LDL-cholesterol lowering effect and its potential effects on long-term liver outcomes, which are being investigated in the MAESTRO-NASH trial. Treatment discontinuation should primarily be considered in case of disease progression or significant adverse events. For Semaglutide, continuation is often justified even in the absence of significant liver improvement, given its well-established benefits on cardiometabolic outcomes, including cardiovascular risk reduction, glycaemic control, weight loss, and kidney disease progression. Therefore, for GLP-1 RA therapy, the decision should integrate both liver-specific response and broader metabolic benefits, particularly in patients with T2D, obesity, or established cardiovascular disease.

3.5. S – Safety monitoring

Regular on-treatment assessment of liver enzyme and function tests should be performed to evaluate drug safety profiles. Although both Resmetirom and Semaglutide are generally well tolerated, gastrointestinal (GI) side effects are common—particularly with Semaglutide. To mitigate these effects, gradual dose escalation for Semaglutide, nutritional adjustments, and patient education are essential. Patients should be encouraged to consume smaller, low-fat meals, avoid overeating, maintain adequate hydration, and regulate dietary fibres intake. For persistent nausea, short-term use of antiemetics may be considered. In cases of diarrhea or constipation, symptomatic management with agents such as loperamide or osmotic laxatives can be helpful. Most GI symptoms tend to resolve over time as patients acclimate to therapy; therefore, follow-up evaluations should be tailored according to clinical tolerance and baseline comorbidities.

Clinical warnings on the use of Resmetirom and Semaglutide are reported in Table 3. Both medications can increase the risk of gallbladder disease, and Semaglutide has been rarely associated with acute pancreatitis; therefore, caution is warranted in patients with known symptomatic cholelithiasis. In the event of biliary colic or suspected pancreatitis, treatment should be discontinued and an appropriate diagnostic work-up promptly undertaken. The routinely use of ursodeoxycholic acid (UDCA) for prevention or management of gallbladder events is not recommended, as its efficacy in this context has not been demonstrated. Additional considerations for Semaglutide therapy include the risk of lean mass loss especially in fragile patients [40,41], which — similarly to what is observed during hypocaloric dietary interventions — represents an expected component of weight reduction. Available evidence indicates that approximately 20–35% of the total weight loss may derive from fat-free mass, with higher proportions reported in older, frail, or sedentary individuals. Although this loss is physiologically inevitable to some extent, it can be minimized through adequate protein intake (≥1.0–1.2 g/kg/day) and regular resistance training, both essential to preserve muscle integrity and metabolic function [42–44]. Patients on Semaglutide treatment and who are waiting for elective surgeries or procedures should be instructed to inform healthcare providers to reduce the risk of pulmonary aspiration resulting from delayed gastric emptying. Semaglutide may cause hypoglycemia when combined with insulin or sulfonylureas and can interfere with absorption of orally administered drugs that have a narrow therapeutic window (e.g., levothyroxine, anticonvulsants, digoxin, oral contraceptives); it should therefore be administered at a different time of day, with therapeutic monitoring when appropriate. In case of severe adverse gastrointestinal side-effects Semaglutide can cause acute kidney injury due to volume depletion, so it is suggested to monitor renal function in patients reporting adverse reactions that could lead to volume depletion. Moreover, its use can lead to increase in heart rate, is not recommended in patients with severe gastroparesis and patients with a history of diabetic retinopathy should be monitored for further complications. Semaglutide should also be discontinued in case of suicidal behaviour and ideation.

4. Treatment options in diabetic and/or obese patients with MASLD without significant/severe liver fibrosis

MASLD/MASH patients who do not meet histological or non-invasive criteria for liver-targeted treatments are often affected by T2D and/or obesity, and should be considered for treatments aimed at reducing the risk of fibrosis progression and cardiovascular or extrahepatic events. Semaglutide in phase 2 and 3 clinical trials, and Tirzepatide in a phase 2 clinical trial, have demonstrated both efficacy and safety in these populations [45–48].

Based on growing evidence showing meaningful improvements in liver-related parameters, both Semaglutide and Tirzepatide could be considered in diabetic and/or obese individuals with MASLD/MASH given their beneficial effects on the metabolic driver of steatosis, although more extensive data concerning the impact on cardiovascular and liver outcomes and longer-term safety data are currently available for Semaglutide.

4.1. Semaglutide and Tirzepatide in non-diabetic obese patients with MASLD

Semaglutide is considered a cornerstone therapy for obesity management. The pivotal STEP 1 trial demonstrated that once-weekly Semaglutide 2.4 mg is effective and safe for inducing sustained weight loss, leading to an average body weight reduction approximately 15% over 68 weeks [42]. A post-hoc analysis showed dose-dependent decreases in ALT levels ranging from 6% to 21% at week 52, with ALT normalization in up to 46% of participants compared with 18% with placebo group [49].

In RCTs involving MASLD patients with overweight/obesity, Semaglutide induced a marked reduction in hepatic steatosis as assessed by MRI-PDFF, with a higher proportion of participants achieving a ≥30% decrease in liver fat content. Treatment also resulted in 18–28% reductions in ALT, aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) compared with placebo, with improvements correlating with reductions in liver fat content [50]. In a controlled crossover study conducted in obese, non-diabetic patients with MASLD, Semaglutide led to 30% relative reduction in liver fat content, with improvements significantly associated with visceral adipose tissue reductions rather than overall weight loss [51]. A post-hoc analysis of the SELECT

trial on obese nondiabetic patients with previous cardiovascular events, conformed the protective effect of Semaglutide versus placebo against cardiovascular events in patients at risk for fibrosis based on the FIB-4 score [52].

Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist, has demonstrated superiority to Semaglutide 2.4 mg in head-to-head comparisons of weight reduction [43,53]. In the SYNERGY-NASH trial, which evaluated patients with histologically-proven MASH, resolution of MASH occurred in a dose-dependent manner in 44% (5 mg), 56% (10 mg), and 62% (15 mg) of Tirzepatide patients *vs.* 10% in the placebo arm [48]. Real-world studies have shown an average weight loss of 12%, accompanied by significant reductions in ALT and AST [54]. Furthermore, Tirzepatide has been associated with a significantly lower incidence of major adverse liver outcomes compared to bariatric surgery (HR 0.32) [55].

4.2. Treatment options in diabetic patients with MASLD

Semaglutide and Tirzepatide are core therapeutic agents for patients with T2D nowadays, also providing benefits on cardiometabolic profiles and reducing kidney risks. Evidence in people with MASLD and T2D shows that Semaglutide efficacy is not attenuated by the presence of T2D, with robust improvements across multiple parameters, including US-based steatosis scores, liver enzymes (34% ALT reduction, 28% AST reduction), HbA1c levels, and visceral adipose tissue. Comparative studies have demonstrated Semaglutide superiority over Dapagliflozin in reducing hepatic steatosis, and subcutaneous Semaglutide has shown greater efficacy than the oral formulation in improving hepatic steatosis (CAP -26.7%), liver stiffness (LSM -20.3%), and liver enzymes (i.e. -27.6% and -17.6% in ALT and AST, respectively) [56]. Data from the SURPASS-3 trial showed that Tirzepatide-treated patients experienced superior reductions in liver fat content compared with those receiving insulin Degludec, with 48% achieving liver fat normalization [57]. Real-world studies have also demonstrated significant improvements in transaminases level after switching to Tirzepatide [49,50]. Combined analysis of histological and non-invasive endpoints from phase 2 and 3 RCT have demonstrated that Semaglutide and Tirzepatide are effective and safe in reducing weight, hepatic steatosis, ALT levels, and in some cases improving fibrosis markers, while maintaining favourable cardiometabolic effects [46,47,54,58,59].

This evidence supports the use of Semaglutide and Tirzepatide in diabetic and/or obese patients with MASLD without significant/severe liver fibrosis.

5. Conclusions

MASLD represents one of the most critical hepatological and public health challenges of our time, with substantial clinical and socio-economic implications. The recent approval of Resmetirom and Semaglutide marks the beginning of a new therapeutic era, shifting management beyond lifestyle interventions toward targeted pharmacological strategies. Nonetheless, optimal patient selection and long-term monitoring remain crucial, particularly through the integration of non-invasive diagnostic tool within multidisciplinary care pathways.

Significant knowledge gaps persist: further evidence is required to refine patient stratification, to better define predictors of treatment response, and —most importantly — to establish standardized strategies for longitudinal monitoring. Addressing these unmet needs will be essential to fully translate the efficacy demonstrated in clinical trials into sustained, real-world benefits for patients, ultimately reshaping the landscape of metabolic liver disease management.

Declaration of competing interest

AAg: speaking and/or advisory board for Gilead, Ipsen, BMS, Novo Nordisk, Madrigal, AbbVie. **AAr:** speaking for Novonordisk, Sanofi, Echosense. **EB:** speaking and/or advisory board for AstraZeneca, Boheringer, Eli Lilly, Inventiva, MSD, Novo Nordisk. **GC:** speaking and/or advisory board for Eisai, Ipsen, AstraZeneca, MSD, Roche, Gilead. **MC:** consultant/speaker bureau for Advanz, Alentis, Albireo, Alfasigma, Amgen, Calliditas, Echosense, Genetic spa, GSK, Ipsen, Intercept, Kowa, Mayloly, Mirun, Perspectum, Zydus; scientific board advisor for Advanz/Intercept, Falk, Gilead, GSK, Ipsen, Kowa, Mirum, Cymabay, Moderna. **RD:** speaking, teaching and advisory board for Gilead Science and AbbVie; consultant and advisory board for Madrigal. **AD** speaking and/or advisory board for Astrazeneca, Eisai, MSD, Novonordisk and Roche. **SDC:** speaking and/or advisory board for AbbVie, Alfasigma. **AG**: consultant and advisory borad for for Roche, Ipsen, Novonordisk, MSD, BMS, AstraZeneca, Alfasigma, Actial, Wellmicro. **GG:** speaking, consulting fee fees and/or travel fees for Chiesi, Alfasigma, Ipsen, Biotest, Novartis. **SG:** speaking and/or advisory board for Gilead. **MI:** consultant for Roche, Roche Diagnostic, Eisai, MSD, AstraZeneca; speaking for Roche, AstraZeneca, Ipsen, Eisai, MSD, Gilead; Travel fees from Roche; research funding by Gilead, Astrazeneca, Roche Diagnostic. **FM:** consultant and/or speaking and/or advisory board and/or travel grant for Aòfasigma, AstraZeneca, Biomarin, Boehringer Ingelheim, Gilead, Gore, Ipsen, Madrigal, MSD/Eisai, Novo Nordisk, Roche. **GM:** speaking for MSD-Eisai, Chiesi, Kedrion, Ipsen, Alfasigma. **MM:** speaking and/or advisory board for Gilead, Ipsen, Novo Nordisk, Alfasigma, AbbVie, Mirum. **LM:** speaking and advisory board for Alexion, Boheringer-Ingelheim, Echosens, GSK, Madrigal, MSD, Mirum, Novonordisk, Reslis Pharma, Siemens Healthineers. **GP:** speaking and/or advisory board and/or consultant for Novo Nordisk, Echosense, Advanz Pharma, Madrigal. **SP:** speaking and/or advisory board for Boeringher, Echosens, Madrigal, Novonordisk, Resalis. **FRP:** speaking and/or consultant and/or travel grant from AstraZeneca, Ipsen, Roche, AbbVie, Gilead, Alfasigma, Mirum. **FR:** research support by Boheringer Ingelheim, Ely Lilly; travel grant by Novo Nordisk; speaking for Novo Nordisk, Eli Lilly, Echosense. **FPR:** speaking, travel grant and advisory board for Gilead, Biotest, Grifols, AbbVie, GSK, Novonordisk. **FT:** consultant for Astrazeneca, Roche, Eisai, BMS, Ipsen; **LV**: speaking for Viatris, Novo Nordisk, GSK; consulting for Novo Nordisk, Pfizer, Boehringer Ingelheim, Resalis, GSK, Almac, AIRNA; travelling by Novo Nordisk. **UVG:** speaking and/or advisory board and/or funding for research by Advanz, Gilead, Ipsen, Mirum, Novo Nordisk, Madrigal, Astra Zeneca. **MV:** speaking and teaching for Gilead, Ipse, AbbVie, Novo Nordisk, Eli Lilly, Kedrion.

Appendix A

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