Clinical Guidelines
Acta Medica Academica 2026;55(2):111-133
DOI: 10.5644/ama2006-124.515

Clinical Practice Guidelines for Adult MASLD in Bosnia and Herzegovina: National Recommendations for Diagnosis, Risk Stratification, and Treatment

Enver Zerem[1], Azra Husić[2], Maja Karin[3], Tanja Glamočanin[4], Mirela Bašić Denjagić[5], Emil Babić[3], Zumreta Bihorac-Kučuk[6], Goran Bokan[4, 7], Nerma Čustović[8], Aida Dumpor[9], Belma Hadžiselimović[10], Admir Kurtcehajic[11], Ljubica Jovandić[4], Predrag Jovanović[5, 12], Amila Mehmedović[13, 14], Nataša Pilipović-Broćeta[15], Dženita Salihefendić[16], Nadža Zubčević[8]

[1]Department of Medical Sciences, The Academy of Sciences and Arts of Bosnia and Herzegovina, Sarajevo, Bosnia and Herzegovina, [2]Department of Gastroenterology and Hepatology, General hospital "Prim. dr Abdulah Nakaš", Sarajevo, Bosnia and Herzegovina, [3]Department of Gastroenterology and Hepatology, University Clinical Hospital Mostar, Mostar, Bosnia and Herzegovina, [4]Internal Medicine Clinic, Department of Gastroenterology and Hepatology, University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina, [5]Department of Gastroenterology and Hepatology, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina, [6]Department of Family Medicine and Academic Specialist in Nutrition, Public Institution Health Center of Canton Sarajevo, Sarajevo, Bosnia and Herzegovina, [7]Faculty of Medicine, University of Banja Luka, Republic of Srpska, Bosnia and Herzegovina, [8]Clinic for Gastroenterohepatology, University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina, [9]Department of Internal Medicine, Cantonal Hospital "Dr. Safet Mujić" Mostar, Mostar, Bosnia and Herzegovina, [10]Internal Department, Department of Gastroenterology, Cantonal Hospital "Dr Irfan Ljubijankić" Bihać, Bihać, Bosnia and Herzegovina, [11]Department of Gastroenterology and Hepatology, Blue Medical Group, Tuzla, Bosnia and Herzegovina, [12]Department of Internal Medicine, Faculty of Medicine, University of Tuzla, Tuzla, Bosnia and Herzegovina, [13]Gastroenterohepatology Clinic, Hepatology Department, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina, [14]Faculty of Health Studies, University of Sarajevo, Sarajevo, Bosnia and Herzegovina, [15]Primary Healthcare Center Banja Luka, Family Medicine Department, Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia and Herzegovina, [16]Private Practice Medicus A, Gračanica, Bosnia and Herzegovina

• Expert Working Group on MASLD in Bosnia and Herzegovina

Correspondence: *zerem@anubih.ba*; Tel.: +387 61 138789

Received: 14 March 2026; **Accepted:** 14 July 2026

Abstract

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease in Bosnia and Herzegovina and a major contributor to liver- and cardiovascular-related morbidity and mortality. These national guidelines provide the first country-specific, evidence-based recommendations for the diagnosis, risk stratification, and management of MASLD, covering the full disease spectrum from steatosis to cirrhosis and its complications. MASLD management is based on a coordinated, stepwise model across primary, secondary, and tertiary healthcare levels, with primary healthcare serving as the central gatekeeper and coordinator of care. Active case-finding of clinically significant fibrosis is emphasized, particularly in high-risk populations, such as individuals with type 2 diabetes mellitus or obesity. Primary healthcare plays a key role in early risk assessment through systematic evaluation of metabolic risk factors and first-line use of simple non-invasive tools, notably the FIB-4 index. A stepwise non-invasive diagnostic algorithm is recommended, with elastography (preferably vibration-controlled transient elastography or 2D shear wave elastography where available) used for further assessment in patients with indeterminate or high-risk results. Lifestyle modification and optimal management of cardiometabolic comorbidities remain the foundations of MASLD treatment. In eligible patients with type 2 diabetes mellitus and/or overweight or obesity, glucagon-like peptide-1 receptor agonists may be considered, while bariatric surgery represents an option for selected individuals with persistent obesity. Advanced MASLD, including cirrhosis, requires multidisciplinary management, surveillance for hepatocellular carcinoma, and evaluation for liver transplantation in cases of decompensation. These guidelines aim to standardize MASLD care in Bosnia and Herzegovina and strengthen the pivotal role of primary healthcare within the national MASLD care pathway.

Key Words: MASLD ▪ Clinical Guidelines ▪ Management ▪ Bosnia and Herzegovina.

Purpose of the Guidelines

These national guidelines provide healthcare professionals in Bosnia and Herzegovina (BA) with a practical, evidence-based framework for the diagnosis, risk stratification, and management of metabolic dysfunction-associated steatotic liver disease (MASLD). These recommendations represent an adaptation of the EASL-EASD-EASO Clinical Practice Guidelines for MASLD (1) to the healthcare setting of BA. Accordingly, the guideline does not independently re-grade the available evidence but relies primarily on the evidence appraisal and recommendation framework established in the source guideline, while adapting diagnostic and therapeutic pathways to local healthcare resources and availability. In addition to international evidence and consensus statements, the recommendations incorporate expert opinions from leading national specialists and are adapted to the specific context of BA, including the availability of approved pharmacological therapies, diagnostic resources, and the organizational structure of primary, secondary, and tertiary healthcare levels. By integrating current scientific evidence with local regulatory, infrastructural, and cost-effectiveness considerations, the guidelines support rational clinical decision-making and efficient use of healthcare resources. They are intended for all healthcare professionals involved in MASLD care, including family physicians, internists, gastroenterologists, endocrinologists, and other relevant specialists. Particular emphasis is placed on the central gatekeeping and coordinating role of primary healthcare as the foundation for early detection, risk stratification, and longitudinal management of MASLD within the national care pathway.

Definition of MASLD

MASLD formerly known as non-alcoholic fatty liver disease (NAFLD), encompasses a broad spectrum of liver disease associated with metabolic dysfunction. It is defined by the presence of hepatic steatosis in individuals with at least one established cardiometabolic risk factor, in the absence of significant alcohol consumption or other secondary causes of hepatic steatosis (1, 2).

The progressive inflammatory form of the disease, termed metabolic dysfunction-associated steatohepatitis (MASH), is characterized histologically by steatosis, hepatocellular ballooning, and lobular inflammation. Clinical prognosis is primarily determined by fibrosis stage rather than by steatosis alone. The disease is closely linked to systemic metabolic dysfunction and is currently regarded as the hepatic manifestation of metabolic syndrome (1).

Overlap Between MASLD and Alcohol-Related Liver Disease: MetALD

The current nomenclature also includes metabolic dysfunction-associated alcohol-related liver disease (MetALD), defined as the coexistence of metabolic dysfunction with alcohol consumption exceeding the thresholds accepted for MASLD diagnosis but not reaching levels traditionally associated with predominant alcohol-related liver disease. Recognition of MetALD reflects the common overlap between metabolic and alcohol-related liver injury and highlights the need to address both metabolic risk factors and alcohol consumption during patient management (1, 2).

Epidemiological Burden, Prevalence, and Natural History of MASLD

MASLD represents a major and growing public health burden worldwide and is increasingly recognized as a significant health concern in BiH (1, 3). Although comprehensive national registries and population-based epidemiological studies are currently lacking, available regional data and the high prevalence of cardiometabolic risk factors suggest that the burden of MASLD in BiH is substantial.

Based on European population studies, the overall prevalence of MASLD in adults is estimated at approximately 30–35% (3-6). Given the comparable or higher prevalence of obesity, type 2 diabetes mellitus (T2D), arterial hypertension, and dyslipidaemia in BiH, a similar prevalence in

the general population is highly plausible. In high-risk groups, particularly individuals with T2D, MASLD prevalence exceeds 60–70%, consistent with data from other European countries (1, 6).

The natural history of MASLD is heterogeneous. While a substantial proportion of individuals remain asymptomatic with stable hepatic steatosis, approximately 10–30% progress to MASH and clinically significant fibrosis over time (1, 5). In patients with T2D and multiple metabolic risk factors, disease progression is markedly accelerated, with advanced fibrosis or MASH reported in up to 40–60% of cases (1, 6). Progressive fibrosis is the strongest predictor of liver-related morbidity and mortality (7, 8).

In BA, advanced stages of MASLD, including cirrhosis and HCC, are increasingly encountered in secondary and tertiary healthcare settings. MASLD is now recognized as a leading cause of cryptogenic cirrhosis and an increasingly important indication for liver transplantation in Europe, a trend that is likely to be mirrored in BiH as diagnostic awareness and case detection improve. Beyond liver-related outcomes, MASLD is associated with increased all-cause and cause-specific mortality, predominantly driven by cardiovascular disease, which represents the leading cause of death in this patient population. The coexistence of MASLD with cardiovascular disease, chronic kidney disease, and other metabolic complications substantially increases healthcare utilization and long-term costs, underscoring the need for early detection and risk stratification, particularly in primary healthcare settings. In addition to cardiovascular and liver-related mortality, accumulating evidence suggests that extrahepatic malignancies contribute substantially to the overall mortality burden associated with MASLD (1, 5).

Pathogenesis and Comorbidities of MASLD

MASLD is a complex, multisystem disorder and represents the hepatic manifestation of systemic metabolic dysfunction. Rather than an isolated liver condition, MASLD reflects the interplay between insulin resistance, dysregulated lipid metabolism, chronic low-grade inflammation, and progressive fibrogenesis, and is tightly linked to cardiometabolic and endocrine comorbidities (1, 9, 10).

Understanding the pathophysiological mechanisms and associated comorbidities of MASLD is essential for appropriate risk stratification and for designing integrated management strategies. This chapter outlines the key pathogenic mechanisms and the major metabolic comorbidities that determine prognosis and guide clinical decision-making.

Pathophysiological Mechanisms of MASLD

At the core of MASLD pathogenesis lies insulin resistance, which drives a cascade of metabolic disturbances within the liver and peripheral tissues. Insulin resistance promotes increased lipolysis in adipose tissue, enhanced hepatic de novo lipogenesis, and impaired export of triglycerides from hepatocytes. The net result is excessive intrahepatic lipid accumulation and hepatocellular lipotoxicity (9, 10).

Lipotoxic stress induces oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress, leading to hepatocyte injury and apoptosis. These processes activate innate immune pathways, including Kupffer cells, and stimulate hepatic stellate cell activation, thereby promoting chronic inflammation and progressive fibrosis. In a subset of patients, this culminates in metabolic dysfunction–associated steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma (1, 10).

Disease susceptibility and progression are further modified by genetic and hormonal factors. Variants in genes such as *PNPLA3*, *TM6SF2*, and *MBOAT7* are associated with increased hepatic fat accumulation, more severe necroinflammation, and accelerated fibrosis, independent of classical metabolic risk factors (11). Hormonal influences (e.g., postmenopausal status) and environmental factors, including sedentary lifestyle, smoking, and diets rich in refined carbohydrates and saturated fats, additionally contribute to disease development and progression (12).

Collectively, these mechanisms support the concept of MASLD as a systemic metabolic disease

with hepatic involvement, a paradigm that underpins modern approaches to screening, prognostication, and integrated care.

MASLD and Metabolic Comorbidities: Clinical Implications

MASLD is a hepatic manifestation of systemic metabolic dysfunction and is frequently accompanied by cardiometabolic comorbidities that adversely affect both overall and liver-related outcomes. As cardiovascular disease remains the leading cause of death in this population, comprehensive cardiometabolic risk assessment and management are essential components of care (1, 13). Table 1 summarizes the wide range of cardiometabolic and systemic comorbidities associated with MASLD and their clinical implications. In the following sections, we focus on those comorbidities with the strongest evidence for impact on disease progression, prognosis, and therapeutic decision-making.

Type 2 Diabetes Mellitus

Type 2 diabetes (T2D) is the most important clinical risk factor for progression from simple steatosis to MASH, advanced fibrosis, cirrhosis, and hepatocellular carcinoma. Approximately 60–70% of patients with T2D have MASLD, and the presence of diabetes roughly doubles the risk of advanced fibrosis (13). Effective glycaemic control is therefore a cornerstone of management. Antidiabetic agents with proven or potential hepatic benefit, such as GLP-1 receptor agonists and SGLT2 inhibitors, are preferred, while pioglitazone may be considered in carefully selected patients with biopsy-proven MASH (1, 14).

Dyslipidemia

Atherogenic dyslipidemia is highly prevalent in MASLD and represents a major driver of cardiovascular morbidity and mortality. Statins are safe across the entire spectrum of MASLD, including compensated cirrhosis, and are strongly recommended for both primary and secondary cardiovascular prevention. Importantly, statin therapy does not exacerbate liver disease and may reduce both cardiovascular and liver-related outcomes (15).

Arterial Hypertension

Arterial hypertension commonly coexists with MASLD as part of the metabolic syndrome and contributes substantially to cardiovascular risk. Adequate blood pressure control is essential for reducing overall cardiovascular morbidity and mortality in patients with MASLD. Management should follow established hypertension guidelines and be individualized according to the patient's overall cardiometabolic profile (16).

Cardiovascular Disease

Cardiovascular disease represents the leading cause of death in patients with MASLD, surpassing liver-related mortality. MASLD should therefore be considered a cardiovascular risk enhancer, warranting aggressive risk factor modification and early preventive strategies. Several studies suggest that MASLD may represent an independent cardiovascular risk factor, although residual confounding and causal pathways remain under investigation (1, 13).

Obesity

Obesity, particularly visceral adiposity, is a central driver of MASLD pathogenesis, promoting insulin resistance, hepatic inflammation, and fibrogenesis. Sustained weight loss remains the most effective intervention for improving hepatic steatosis, necroinflammation, and fibrosis. Lifestyle modification is first-line therapy, while pharmacological and surgical weight-loss strategies may be appropriate in selected patients with obesity and metabolic complications (1, 17).

Integrated Clinical Perspective

All patients with MASLD should undergo systematic evaluation for metabolic comorbidities, including T2D, dyslipidemia, hypertension, and

Table 1. Key Cardiometabolic Comorbidities Associated with MASLD* and Their Clinical Implications

MASLD*- associated comorbidity	Relationship with MASLD*	Key clinical implications
Type 2 diabetes mellitus	Key risk factor for progression to MASH†, fibrosis, cirrhosis, HCC‡	High-priority group for fibrosis risk stratification and proactive liver assessment
Obesity (visceral adiposity)	Key driver of steatosis, inflammation, fibrogenesis	Sustained weight loss key to liver improvement
Dyslipidemia	Nearly universal; major determinant of CV§ risk	Reduce CV§ risk: statins safe, recommended
Arterial hypertension	Common MetS‖ component in MASLD*	Adequate BP¶ control reduces CV§ morbidity
Metabolic syndrome	Reflects systemic metabolic dysfunction in MASLD*	Predicts liver disease progression and CV§ events
Cardiovascular disease	Leading cause of death in MASLD*	CV§ risk management core to MASLD*
Chronic kidney disease	Frequently coexists due to shared metabolic risk factors	Linked to higher overall and liver-related mortality
Polycystic ovary syndrome	Associated with IR** and increased MASLD* prevalence	Assess liver in PCOS†† women with metabolic risk
Obstructive sleep apnea	IH‡‡ drives inflammation and fibrosis	Associated with more severe steatosis and fibrosis
Hypothyroidism	Alters lipid metabolism and energy homeostasis	May worsen hepatic steatosis and metabolic profile

*Metabolic dysfunction–associated steatotic liver disease; †Metabolic dysfunction–associated steatohepatitis; ‡Hepatocellular carcinoma; §Cardiovascular; ‖Metabolic dysfunction-associated alcohol-related liver disease; ¶Blood pressure; **Insulin resistance; ††PCOS – Polycystic ovarian syndrome; ‡‡Intermittent hypoxia.

obesity. Conversely, individuals with metabolic syndrome or T2D should be proactively assessed for MASLD and for the presence of advanced liver fibrosis using validated non-invasive tools, as outlined in subsequent diagnostic chapters (1, 9).

An integrated, multidisciplinary approach—linking primary care physicians, endocrinologists, cardiologists, and hepatologists—is essential. Optimal control of cardiometabolic comorbidities not only reduces overall mortality but also represents a fundamental component of effective liver disease management.

Management of cardiometabolic comorbidities should be initiated according to standard clinical indications irrespective of fibrosis stage, as cardiovascular disease remains the leading cause of mortality in patients with MASLD. Treatment decisions should be guided by established cardiovascular, metabolic, and endocrine indications (1).

Diagnosis and Differential Diagnosis of MASLD

The diagnosis of MASLD requires objective evidence of hepatic steatosis in the presence of metabolic risk factors, following the exclusion of alternative causes of liver disease, particularly significant alcohol consumption. A structured, stepwise diagnostic approach is recommended to ensure diagnostic accuracy, appropriate risk stratification, and rational use of non-invasive and invasive diagnostic tools (1, 2, 18-20).

Diagnostic Criteria for MASLD

MASLD is diagnosed when all of the following conditions are fulfilled:

- Evidence of hepatic steatosis (by imaging, validated serum-based steatosis scores and composite non-invasive assessment tools, or histology).
- Presence of at least one cardiometabolic risk factor (overweight/obesity, insulin resistance and its clinical manifestations, particularly type 2 diabetes mellitus, dyslipidemia, or arterial hypertension).
- Absence of other primary causes of steatotic or chronic liver disease.

Initial Clinical Evaluation

Medical History and Physical Examination

A comprehensive medical history should focus on:
- Quantification of alcohol intake; alcohol consumption exceeding accepted thresholds should prompt consideration of alcohol-related liver disease or mixed etiologies (1, 2).
- Presence and duration of metabolic comorbidities (type 2 diabetes, obesity, and metabolic syndrome).
- History of medication use, including drugs associated with steatosis or steatohepatitis (e.g. amiodarone, methotrexate, tamoxifen).
- Family history of liver disease, diabetes, or hereditary metabolic disorders. Physical examination should assess signs of insulin resistance, obesity distribution, and features of chronic liver disease.

Laboratory Assessment

Baseline laboratory evaluation should include:
- Liver enzymes: ALT, AST, gamma-glutamyl transferase (GGT), and alkaline phosphatase.
- Platelet count, as a surrogate marker of portal hypertension and advanced fibrosis.
- Metabolic profile: fasting glucose or HbA1c, lipid profile.
- Additional tests as indicated: ferritin, transferrin saturation, autoimmune markers, viral hepatitis serology.

Importantly, normal aminotransferase levels do not exclude MASLD, MASH, or advanced fibrosis, and liver enzyme levels correlate poorly with disease severity (18, 21-23).

Imaging for Detection of Hepatic Steatosis

Ultrasound

Abdominal ultrasound is recommended as the first-line imaging modality for detecting hepatic steatosis due to its wide availability, safety, and cost-effectiveness, particularly in primary and secondary care settings in BiH. Conventional ultrasonography demonstrates sensitivity of approximately 85% and specificity of approximately 94% for moderate-to-severe hepatic steatosis but performs less reliably in mild steatosis and severe obesity (1, 22, 24).

Advanced Imaging

Magnetic resonance imaging–proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE) should be reserved for specialized centers and selected cases where non-invasive tests are inconclusive or when advanced disease is suspected. MRI-PDFF is currently regarded as the most accurate non-invasive modality for quantifying liver fat, while magnetic resonance elastography demonstrates excellent diagnostic performance for advanced fibrosis (AUROC frequently >0.90). Their use is largely limited by availability and cost (25, 26).

Elastography

In patients with indeterminate or high-risk serum fibrosis scores, vibration-controlled transient elastography (VCTE) remains the preferred second-line test because of its extensive validation for the assessment of significant and advanced fibrosis. However, two-dimensional shear wave elastography (2D-SWE) demonstrates comparable diagnostic performance and may be used as an alternative where appropriate expertise and equipment are available (2, 27-29). Elastography also provides prognostic information and supports longitudinal disease monitoring. In patients with MASLD, liver stiffness measurement obtained by VCTE can be used for fibrosis risk stratification. Although cut-off values vary among studies and according to the clinical context, liver stiffness values below approximately 8 kPa generally indicate a low probability of advanced fibrosis, values between 8 and 12 kPa suggest an increased likelihood of significant or advanced fibrosis, whereas values above 12 kPa are associated with a high probability of advanced fibrosis or cirrhosis and warrant specialist evaluation (1, 22).

Non-Invasive Assessment of Liver Fibrosis

Serum-Based Fibrosis Scores

Risk stratification for advanced fibrosis should be performed using validated non-invasive scores, including:

- FIB-4 index.
- NAFLD Fibrosis Score (NFS).
- Enhanced Liver Fibrosis (ELF) test, where available.

These tools are recommended as first-step triage tests to identify patients at low risk of advanced fibrosis and to reduce unnecessary referrals (2, 22, 23, 27, 28).

The diagnostic performance of commonly used non-invasive fibrosis assessment tools varies according to the fibrosis stage being evaluated, selected cut-off values, and study population characteristics. Nevertheless, these tools have been extensively validated and are recommended by major international guidelines as part of a stepwise approach to fibrosis risk stratification. Table 2 summarizes the overall diagnostic performance of the most frequently used non-invasive tests in patients with MASLD (1, 22, 26-33).

Among currently available non-invasive modalities, simple serum-based scores such as FIB-4 and NFS are primarily useful for excluding advanced fibrosis in low-risk populations and represent appropriate first-line tools in primary care. Elastography-based methods, particularly VCTE and magnetic resonance elastography, provide greater diagnostic accuracy for fibrosis staging and are generally used in secondary and tertiary healthcare settings. These complementary characteristics support the stepwise diagnostic algorithm proposed in this guideline, balancing diagnostic accuracy with resource availability and cost-effectiveness (1, 2, 22).

Role of Liver Biopsy in MASLD

Liver biopsy is not routinely indicated for the diagnosis of MASLD but may be considered in selected patients. It should be considered when non-invasive tests provide discordant results, when alternative liver diseases cannot be excluded, or when histological confirmation of MASH may influence eligibility for disease-specific pharmacological therapy (1).

Differential Diagnosis of MASLD

A thorough differential diagnosis is mandatory before establishing MASLD, as hepatic steatosis may occur in several other liver diseases. Conditions that must be excluded include:

- Alcohol-related liver disease (ALD) and metabolic dysfunction-associated alcohol-related liver disease (MetALD)
- Chronic viral hepatitis B and C
- Autoimmune hepatitis
- Cholestatic liver diseases (primary biliary cholangitis, primary sclerosing cholangitis)
- Wilson disease
- Hereditary hemochromatosis
- Drug-induced liver injury
- Other genetic or metabolic liver disorders

Table 2. Diagnostic Performance of Commonly Used Non-invasive Tests for Liver Fibrosis in MASLD*

Test	Primary Clinical Role	Approximate AUROC† for Advanced Fibrosis (F≥3)
FIB-4 Index‡	First-line risk stratification/exclusion of advanced fibrosis	0.76–0.84
NFS§	First-line risk stratification/exclusion of advanced fibrosis	0.72–0.82
VCTE/FibroScan‖	Secondary assessment of fibrosis severity	0.85–0.90
MRE¶	Advanced fibrosis assessment	0.90–0.95
FAST Score**	Identification of patients with at-risk MASH††	0.80–0.85

*Metabolic dysfunction–associated steatotic liver disease; †Area under the receiver operating characteristic curve; ‡Fibrosis-4 index; §Non-alcoholic fatty liver disease fibrosis score; ‖Vibration-controlled transient elastography; ¶Magnetic resonance elastography; **FibroScan-AST score; ††Metabolic dysfunction-associated steatohepatitis. *AUROC values are approximate ranges derived from representative validation studies and may vary according to fibrosis stage, cut-off values, and study population.*

Appropriate serological, biochemical, imaging, and genetic testing should be performed based on clinical suspicion and patient phenotype (1, 18, 21).

Risk Stratification and Follow-Up

Risk stratification is a cornerstone of MASLD management, as the stage of liver fibrosis represents the strongest predictor of liver-related outcomes and overall mortality. Accordingly, a pragmatic, non-invasive, stepwise risk stratification algorithm is recommended, particularly in the primary care setting, to identify patients who require specialist referral and structured follow-up (1, 2, 25).

Risk Stratification in Primary Care

Step 1: Serum-Based Fibrosis Assessment (FIB-4)

The fibrosis-4 (FIB-4) index should be used as the initial screening tool in patients with MASLD (2, 23-26, 29).

- A FIB-4 value <1.3 reliably excludes advanced fibrosis in individuals younger than 65 years, whereas a threshold <2.0 should be used in patients aged ≥65 years.
- FIB-4 values between 1.3 and 2.67 (<65 years) should be considered indeterminate and require further evaluation.
- FIB-4 values >2.67 indicate a high probability of advanced fibrosis and warrant specialist assessment.

Step 2: Elastography

Patients with indeterminate or high-risk FIB-4 values should undergo liver stiffness measurement using validated elastography techniques, such as vibration-controlled transient elastography (VCTE) or two-dimensional shear wave elastography (2D-SWE) (2, 25, 29-34).

Management of Advanced Fibrosis (F3–F4)

Patients with suspected advanced fibrosis based on non-invasive testing (e.g., FIB-4 >2.67 and/or liver stiffness values compatible with F3-F4 fibrosis) and those with confirmed advanced fibrosis or cirrhosis should be referred to specialized hepatology care (1, 35).

Rationale for the Stepwise Approach

This non-invasive, stepwise strategy:

- Enables early identification of patients at highest risk for liver-related complications,
- Reduces unnecessary liver biopsies,
- Optimizes the use of healthcare resources,
- Strengthens the role of primary care in long-term MASLD management.

Prevention and Treatment of MASLD

Prevention and management of MASLD require early identification of individuals at risk and a comprehensive, long-term strategy targeting metabolic dysfunction, lifestyle factors, and liver-specific disease progression (1, 2, 18). Since cardiovascular disease represents the leading cause of mortality in patients with MASLD, preventive and therapeutic approaches must prioritize both hepatic and systemic cardiometabolic outcomes (36, 37). Public health strategies in Bosnia and Herzegovina should emphasize population-level interventions addressing obesity, type 2 diabetes mellitus (T2D), unhealthy dietary patterns, physical inactivity, and smoking, supported by structured patient education and access to nutritional counseling (2, 38). Key strategies for MASLD prevention and treatment are shown in Table 3.

Non-pharmacological Treatment (Lifestyle Intervention)

Lifestyle modification is the cornerstone of MASLD management and should be recommended to all patients, regardless of disease severity or concomitant pharmacological treatment (1, 2, 18).

Weight reduction

- A ≥5% reduction in body weight is associated with a significant decrease in hepatic steatosis.

Table 3. Strategies for the Prevention and Treatment of MASLD*

Category	Specific Measure/Intervention		Key Goals/Effects	Key Message
Core principles	Early identification and long-term strategy		Targeting metabolic dysfunction, liver disease progression, and CV† risk	Multidisciplinary approach
Public health strategies	Population-level interventions		Addressing obesity, T2D‡, unhealthy diet, physical inactivity, and smoking	Education and structured prevention programs
Non-pharmacological treatment	Cornerstone for all patients (Lifestyle intervention)	Weight reduction	≥5%: Reduces hepatic steatosis ≥7–10%; Improves steatohepatitis ≥10%; May induce fibrosis regression	Individualized approach is essential
		Dietary measures	Mediterranean hypocaloric style diet improves metabolic control	Reduce free sugars and ultra-processed foods
		Physical activity	Aerobic and resistance exercise improve liver enzymes, reduce hepatic fat, and boost insulin sensitivity	Regular activity is recommended
		Additional factors	Moderate coffee consumption and smoking cessation	Improve metabolic control
Management of comorbidities	Control of T2D‡ hypertension, dyslipidemia, and obesity		Reduces overall CV† risk and indirectly slows liver disease progression	Statins should be prescribed for CV† indications
MASLD*-directed pharmacotherapy	Patients with fibrosis (≥F2) or high risk of progression		Always complements, does not replace, lifestyle modification.	It is used when lifestyle interventions fail
Drugs for comorbidities (not MASLD*-specific)	GLP-1 Receptor Agonists§ (e.g., semaglutide)		Weight loss; steatosis/MASH‖ improvement	Not approved as MASLD*-specific therapy, used for T2D‡
	Pioglitazone		Improves MASH‖ histology, especially in T2D‡. Only for biopsy-proven patients	Limited by side effects (weight gain, edema)
	SGLT2¶ Inhibitors		May reduce hepatic fat. Safe in T2D‡	Not approved as specific MASLD*/MASH‖ therapy
	Metformin		Improves insulin sensitivity	No benefit in liver histology
Agents available for MASLD* in BiH	Ursodeoxycholic acid		Improves liver enzymes and inflammatory markers	Useful in early stages (F0-F2) with elevated enzymes
	Vitamin D		Correction of deficiency may improve metabolic and inflammatory profiles	Safe, inexpensive supportive therapy
	Vitamin E (α-tocopherol)		Histological benefit in non-diabetic, non-cirrhotic biopsy-proven MASH‖	Not for routine use due to long-term safety concerns
Emerging and non-available therapies	Resmetirom (THR-β** agonist)		Phase III trials show improvement in steatohepatitis and fibrosis	Currently not available on the market in BA
	Semaglutide 2.4 mg			
	Bile acid-targeting agents (e.g., OCA††)		Antifibrotic effects without proven clinical benefit	Not part of routine MASLD* management
Interventional and surgical approaches	Endoscopic bariatric Therapy		Weight loss (~10–12% at 6 months)	In obese patients refractory to lifestyle modifications
	Bariatric Surgery		Sustained weight loss, improvement of comorbidities and liver histology	For selected obese patients with compensated cirrhosis
	Liver transplantation		Treatment for end-stage cirrhosis and hepatocellular carcinoma	Post-transplant management focuses on metabolic risk control

*Metabolic dysfunction-associated steatotic liver disease; †Cardiovascular; ‡Type 2 Diabetes; §Glucagon-like peptide-1 receptor agonists; ‖Metabolic dysfunction-associated steatohepatitis; ¶Sodium-glucose co-transporter-2 inhibitors; **Thyroid hormone receptor-β ††Obeticholic Acid.

– ≥7–10% weight loss improves steatohepatitis (MASH) and necroinflammatory activity.
– ≥10% weight loss may induce fibrosis regression in selected patients (39-42).

Dietary measures

– Hypocaloric diet individualized according to metabolic needs.
– Preference for Mediterranean-style dietary patterns.
– Reduction of free sugars, fructose-containing beverages, and ultra-processed foods (42-44).

Physical activity

– Regular aerobic and resistance exercise improves liver enzymes, reduces hepatic fat content, and enhances insulin sensitivity, even in the absence of significant weight loss. At least 150–300 minutes of moderate-intensity aerobic activity per week, combined with resistance training 2–3 times weekly, is recommended (45-47).

Additional lifestyle factors

– Moderate coffee consumption is associated with hepatoprotective effects, including reduced fibrosis progression. Moderate coffee consumption generally refers to approximately 2–3 cups daily (48, 49).
– Smoking cessation is strongly recommended due to its adverse metabolic and cardiovascular effects (50, 51).

Integrated Management of Metabolic Comorbidities

Optimal control of metabolic comorbidities is a fundamental component of MASLD management and should be pursued in all patients, regardless of fibrosis stage, as cardiovascular disease is the leading cause of mortality in these patients. However, management of cardiometabolic risk factors should be conceptually distinguished from MASLD-specific pharmacotherapy (1, 18).

– Type 2 diabetes mellitus, hypertension, dyslipidaemia, and obesity should be managed according to established clinical practice guidelines.
– Pharmacological treatment of metabolic comorbidities should not be withheld because of a diagnosis of MASLD and should follow standard cardiovascular, metabolic, and endocrine indications.
– Although these interventions are not considered MASLD-specific therapies, effective cardiometabolic risk reduction may slow liver disease progression and reduces cardiovascular and overall mortality (52).

Pharmacological Therapy for MASLD in Bosnia and Herzegovina

Pharmacological therapy should be considered only in patients with confirmed MASLD and significant fibrosis (≥F2) or in those at high risk of disease progression (age >50 years, T2D, metabolic syndrome, persistently elevated ALT), particularly when structured lifestyle interventions fail (1, 2, 18). Pharmacological treatment must always complement, not replace, lifestyle modification and optimal management of metabolic comorbidities.

Drugs Used for Comorbidities (Not MASLD-Specific Therapy)

Several medications commonly prescribed in patients with MASLD provide metabolic and indirect hepatic benefits. However, they are not currently considered MASLD-specific disease-modifying therapies and should be prescribed according to their approved indications:

– ***Statins***
Statins are safe across the MASLD spectrum, including in patients with compensated cirrhosis, and should not be withheld when indicated for cardiovascular risk reduction. They do not improve steatosis, steatohepatitis, or fibrosis sufficiently to justify a MASLD-specific indication. Although observational studies suggest a potential reduction in progression to advanced fibrosis, cirrhosis, and liver-related

complications, current evidence remains insufficient to recommend statins specifically for the treatment of MASLD (53-55).

- ***Metformin***
  Metformin improves insulin sensitivity and glycaemic control and should be used in patients with type 2 diabetes mellitus according to standard diabetes care. However, it has not demonstrated meaningful histological benefit in MASLD and should not be used specifically for the treatment of MASLD (56, 57).
- ***GLP-1 receptor agonists (e.g., semaglutide, liraglutide)***
  GLP-1 receptor agonists used for the treatment of type 2 diabetes mellitus (e.g., semaglutide up to 1.0 mg, liraglutide) promote weight loss and improve glycaemic and cardiometabolic control. Although clinical trials have shown reductions in hepatic steatosis and increased rates of MASH resolution, consistent antifibrotic effects have not been established. Accordingly, they are not currently recommended as MASLD-specific pharmacotherapy. Higher-dose semaglutide (2.4 mg) used for obesity treatment is discussed separately (58-60).
- ***Sodium-glucose co-transporter-2 inhibitors (SGLT2 inhibitors)***
  SGLT2 inhibitors are safe in patients with MASLD and type 2 diabetes mellitus and may reduce hepatic fat content while providing cardiovascular and renal benefits. They should be prescribed according to diabetes indications but are not approved as MASLD/MASH-specific therapy (61, 62).
- ***Pioglitazone***
  Pioglitazone has demonstrated histological benefits in patients with MASH, particularly those with type 2 diabetes mellitus. However, its use is limited by adverse effects, including weight gain, fluid retention, and increased risk of heart failure. Pioglitazone may be considered in carefully selected patients with biopsy-confirmed MASH but is not recommended for routine treatment of MASLD (63).

Pharmacological Agents Available for MASLD Management in BA

At present, pharmacological options available for use in MASLD management in BA are limited. Three agents are available and may be used in selected patients as part of an integrated, individualized treatment strategy: ursodeoxycholic acid (UDCA), vitamin D, and vitamin E. Importantly, none of these agents can be considered disease-modifying therapy for MASLD, and their use should always complement lifestyle intervention and optimal management of metabolic comorbidities.

Ursodeoxycholic Acid (UDCA)

Ursodeoxycholic acid (UDCA) is a naturally occurring, hydrophilic bile acid with well-established anti-inflammatory, immunomodulatory, antioxidant, and anti-apoptotic properties. The biological effects of UDCA may be more relevant during earlier stages of MASLD, when hepatocellular injury and inflammatory activity predominate, although convincing evidence of disease modification remains lacking (63-65). Multiple randomized controlled trials and meta-analyses have consistently demonstrated that standard-dose UDCA (10–15 mg/kg/day) leads to significant reductions in serum aminotransferases (ALT and AST) within 1–6 months, while maintaining an excellent safety and tolerability profile (65-70). In addition, UDCA therapy is associated with a reduction in gamma-glutamyl transferase (GGT) levels in patients with MASLD (66, 67), a finding of clinical relevance given that GGT is an independent predictor of liver-related, cardiovascular, and all-cause mortality (71, 72).

Beyond liver enzyme normalization, UDCA may exert favorable effects on metabolic and cardiovascular risk factors, including total and LDL cholesterol and glycemic parameters—benefits not consistently achieved with lifestyle intervention alone. These pleiotropic effects may improve the overall cardiometabolic risk profile and facilitate adherence during the early phase of lifestyle

modification, thereby reinforcing the rationale for UDCA use in carefully selected patients with active biochemical disease (68, 69, 73, 74). Despite these consistent biochemical and metabolic improvements, evidence supporting a clinically meaningful antifibrotic effect of UDCA remains inconsistent and largely inconclusive (67, 68, 70). Consequently, the therapeutic benefit of UDCA appears to be limited to early disease stages, with minimal or no efficacy in patients with advanced fibrosis or established MASH, where structural liver damage predominates.

Clinical position: Current evidence does not support UDCA as a disease-modifying therapy for MASLD or MASH, as consistent histological improvement and antifibrotic effects have not been demonstrated. However, owing to its favourable safety profile and consistent biochemical effects, UDCA may be considered as an adjunct to lifestyle-based management in selected patients, particularly when improvement of liver biochemical parameters is a therapeutic goal (F0-F2).

Vitamin E

Vitamin E (α-tocopherol, 800 IU/day) has demonstrated histological benefit in carefully selected patients with biopsy-proven steatohepatitis who do not have diabetes or cirrhosis (75). Despite these findings, its use in routine clinical practice remains limited due to unresolved concerns regarding long-term safety, including potential associations with prostate cancer, hemorrhagic stroke, and increased all-cause mortality (76). Consequently, vitamin E should not be recommended for routine treatment of MASLD, but may be considered on an individual basis in highly selected, non-diabetic, non-cirrhotic patients after careful assessment of potential benefits and risks. In this context, combination therapy with UDCA and antioxidant supplementation has been shown to be generally well tolerated and associated with sustained improvements in liver biochemistry; however, evidence from comparative studies indicates that while vitamin-based antioxidant therapy may improve fibrosis, it does not significantly reduce GGT levels or inflammatory activity, and overall data remain insufficient to support routine use, restricting such combination approaches to selected patients under specialist supervision (77-79).

Vitamin D

Vitamin D deficiency is highly prevalent among patients with MASLD and is associated with insulin resistance, low-grade inflammation, and fibrosis progression. Vitamin D supplementation is safe, inexpensive, and widely accessible in Bosnia and Herzegovina (80). Correction of vitamin D deficiency should be considered part of general metabolic health management rather than MASLD-specific treatment. Although vitamin D cannot be regarded as MASLD-specific therapy, correction of documented deficiency may improve metabolic and inflammatory profiles and should be considered supportive treatment, particularly in patients with coexisting metabolic dysfunction (81).

Emerging, Experimental, and Currently Non-Available Therapies

Several emerging pharmacological therapies for MASLD/MASH show promising mechanistic and histological effects but remain investigational or unavailable for routine clinical use.

– Resmetirom, a selective thyroid hormone receptor-β (THR-β) agonist, has demonstrated significant histological efficacy in patients with non-cirrhotic MASLD/MASH and moderate to advanced fibrosis (predominantly stages F2–F3) in phase III registration trials conducted over a 52-week treatment period. Compared with placebo, resmetirom achieved higher rates of both steatohepatitis resolution and fibrosis improvement, accompanied by consistent reductions in liver enzymes and atherogenic lipid parameters. Adverse events were predominantly mild to moderate and mainly gastrointestinal in nature. On the basis of these findings, derived from a manufacturer-sponsored phase III registration trial, resmetirom received accelerated

(conditional) regulatory approval by the U.S. Food and Drug Administration (FDA) in March 2024, with a weight-based dosing regimen of 80–100 mg/day (82). Current evidence suggests that the most appropriate candidates for treatment are carefully selected non-cirrhotic patients with MASH and fibrosis stages *F2–F3*. Nevertheless, despite these encouraging results, the drug is not currently available on the local market, and important uncertainties remain regarding its long-term impact on hard clinical outcomes, optimal treatment duration, durability of histological response, and reliable predictors of treatment benefit. Accordingly, the definitive clinical positioning of resmetirom in MASLD management has yet to be fully established, and routine incorporation into national treatment pathways cannot currently be recommended (83-86).

- Bile acid–targeting strategies (FXR-, TGR5-, and FGF19-mediated pathways) represent a biologically plausible therapeutic direction, as bile acids act as central regulators of lipid and glucose metabolism, inflammation, fibrogenesis, and the gut–liver axis. Modulation of bile acid signaling and microbiota composition may provide indirect metabolic benefits, particularly when integrated into multimodal treatment approaches (87-90).
- Among bile acid-based agents, obeticholic acid (OCA) demonstrated antifibrotic and biochemical effects in clinical trials. However, concerns regarding safety, particularly pruritus and adverse lipid profile changes, together with the absence of demonstrated clinical outcome benefits, have limited its regulatory acceptance and routine clinical use. Consequently, OCA is not currently considered part of standard MASLD management and is mentioned here only in the context of bile acid-targeted therapeutic development (1, 91, 92). Tauroursodeoxycholic acid and other experimental bile acid derivatives (e.g. norUDCA, cilofexor, tropifexor, INT-767) remain in early or mid-stage development, with insufficient evidence to support routine clinical use (93-98).
- Recent phase III data from the ESSENCE trial have shown that once-weekly semaglutide 2.4 mg produces robust improvements in liver histology in adults with MASH and moderate to advanced fibrosis, demonstrating both higher rates of MASH resolution and clinically meaningful fibrosis improvement compared with placebo at 72 weeks. These results supported accelerated (conditional) approval by the FDA of Wegovy® (semaglutide 2.4 mg) for the treatment of non-cirrhotic MASH with fibrosis stages F2–F3 in adults, in combination with lifestyle interventions, representing the first GLP-1 receptor agonist to receive a liver-specific indication in this population (99). Current evidence suggests that the most appropriate candidates for treatment are carefully selected adults with non-cirrhotic MASH and fibrosis stages F2–F3, particularly in the presence of overweight, obesity, or other cardiometabolic comorbidities. Nevertheless, confirmatory long-term outcome data and broader regulatory approvals (EMA: CHMP positive opinion; European Commission decision pending) are still awaited, and its definitive role within national treatment pathways remains to be established (100-102). Dual and triple incretin receptor agonists, including agents such as tirzepatide and survodutide, remain investigational in MASLD/MASH and cannot currently be recommended outside clinical trials, as no liver-specific indication has yet been formally approved (103-105).

Interventional and Surgical Approaches

Endoscopic Therapy

Endoscopic bariatric interventions may be considered in selected patients with obesity who do not achieve sufficient weight loss with lifestyle modification alone. Among these, intragastric balloon placement has been associated with short-term weight reduction and improvements in metabolic parameters, including hepatic steatosis in some studies. However, the available evidence

in MASLD is limited, and the durability of these benefits after balloon removal remains uncertain. These procedures should be avoided in patients with esophageal or gastric varices or clinically significant portal hypertension. Available evidence from small studies suggests an average weight reduction of approximately 10–12% at 6 months following treatment (106, 107). In carefully selected patients with obesity and MASLD-associated compensated cirrhosis, bariatric surgery may be considered following thorough multidisciplinary assessment. Indications generally include a body mass index (BMI) ≥40 kg/m², ≥35–40 kg/m² in the presence of obesity-related comorbidities, or ≥30–35 kg/m² in patients with poorly controlled type 2 diabetes and/or arterial hypertension, provided there are no features of decompensated liver disease. Emerging evidence suggests that bariatric surgery may result in fibrosis regression and even partial reversal of compensated cirrhosis in selected patients, although careful patient selection remains essential (107, 108).

Liver Transplantation

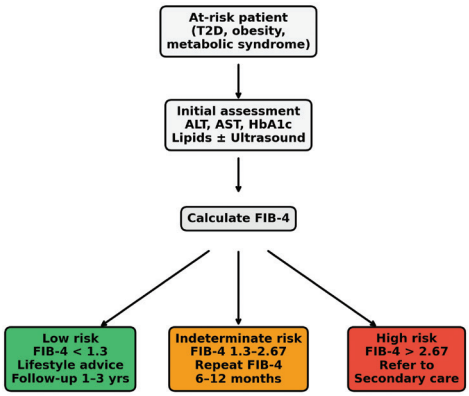
MASLD-related cirrhosis and hepatocellular carcinoma (HCC) are rapidly emerging as leading indications for liver transplantation worldwide. In appropriately selected patients, liver transplantation provides a significant survival benefit, with post-transplant outcomes comparable to those of non-MASLD recipients (109, 110). Although recurrence of metabolic liver disease after transplantation is common, disease progression is typically slow and rarely compromises graft survival. Timely referral to a transplant center is essential, particularly for patients with decompensated cirrhosis or those developing HCC within accepted transplant criteria. Given the high prevalence of metabolic comorbidities, sarcopenia, and frailty in MASLD/MASH, routine assessment during transplant evaluation is recommended, as early identification and targeted interventions may improve peri- and post-transplant outcomes (111). Surveillance for HCC plays a critical role in maintaining transplant eligibility. In patients with MASLD-related cirrhosis, abdominal ultrasound combined with alpha-fetoprotein (AFP) measurement every 6 months is recommended (104). Cross-sectional imaging (CT or MRI) should be reserved for further characterization of lesions detected on ultrasound. Treatment strategy and liver transplant eligibility are determined according to established staging systems and transplant criteria, including the Barcelona Clinic Liver Cancer (BCLC) classification and Milan criteria (112).

Role of Health Care System Levels in the Management of MASLD

Effective management of MASLD requires an integrated, stepwise approach across primary, secondary, and tertiary levels of healthcare. Given the high prevalence of MASLD, its close association with cardiometabolic disorders, and its frequently asymptomatic course, primary healthcare plays a central gatekeeping and coordinating role within the national MASLD care pathway (1, 2).

Primary healthcare is pivotal for early identification of individuals at risk, initiation of first-line non-invasive fibrosis risk stratification using simple tools such as the FIB-4 index, implementation of lifestyle and behavioral interventions, and long-term follow-up of patients at low risk of advanced fibrosis (1, 2, 22). In addition, primary care ensures optimal management of metabolic comorbidities and coordinates timely referral to specialist care for patients with indeterminate or high-risk non-invasive test results (1, 2, 36). The central role of primary healthcare as the first point of contact for MASLD detection and risk stratification is summarized in Figure 1.

Secondary healthcare provides diagnostic refinement and specialist management for patients referred from primary care. Its core responsibilities include confirmation of disease stage using advanced non-invasive methods, particularly vibration-controlled transient elastography, identification of patients with significant or progressive fibrosis, and supervision of pharmacological therapies where indicated, in close collaboration with primary healthcare (1, 2, 22, 31).



At-risk individuals (obesity, type 2 diabetes, or metabolic syndrome) are evaluated in primary care using routine laboratory tests, with or without liver ultrasound, followed by first-line fibrosis risk stratification using the fibrosis-4 (FIB-4) index. Patients at low risk (FIB-4 <1.3; green) are managed with lifestyle counselling and cardiometabolic risk control, with periodic reassessment, whereas those with indeterminate risk (FIB-4 1.3–2.67; amber) require closer follow-up. Patients at high risk (FIB-4 >2.67; red) are referred for specialist evaluation.

Figure 1. Primary healthcare algorithm for MASLD management.

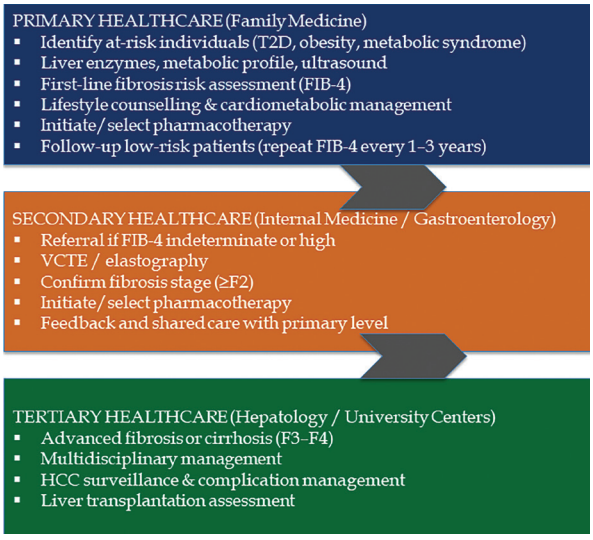


Figure 2. Organization of MASLD care across primary, secondary, and tertiary healthcare levels in BA.

Tertiary healthcare is reserved for patients with advanced fibrosis, cirrhosis, or MASLD-related complications and is responsible for comprehensive multidisciplinary management, surveillance for hepatocellular carcinoma, use of advanced diagnostic modalities when required, and assessment for liver transplantation where appropriate (1, 8, 35). Strengthening primary healthcare as the foundation of MASLD management is essential to improve early detection of advanced fibrosis, optimize healthcare resource utilization, and reduce liver-related and cardiovascular morbidity and mortality in BiH (3, 4, 36). The organization and coordination of MASLD management across primary, secondary, and tertiary healthcare levels in BiH are summarized in Figure 2.

Referral from primary to secondary care is recommended in patients with FIB-4 values above the established low-risk threshold, indeterminate non-invasive test results, persistently elevated liver enzymes, or suspicion of advanced fibrosis. Referral to tertiary care is recommended in patients with confirmed advanced fibrosis, cirrhosis, portal hypertension, hepatocellular carcinoma, or when consideration of advanced pharmacological, bariatric, or transplant-related interventions is required.

The role of Public Health and Prevention in the Management of MASLD

1. Education and support in primary health care:
   - Developing patient education programs to increase awareness of MASLD, risk factors and the importance of early disease recognition.
   - Incorporating strategies to encourage lifestyle changes through educational workshops, support groups and self-help materials.
2. Formalized care pathways:
   - Defining clear criteria and thresholds for the referral process between primary, secondary and tertiary health care.
   - Creating multidisciplinary teams that will collaborate at different levels and ensure an integrated approach to patients with MASLD. Primary care should serve not only as the entry point for diagnosis and risk stratification but also as the central setting for structured lifestyle intervention. Educational programmes, dietary counselling, physical activity promotion, and

behavioural support strategies should be integrated whenever feasible to facilitate long-term adherence to lifestyle modification. Given the high prevalence of obesity, type 2 diabetes, hypertension, and sedentary lifestyle patterns in Bosnia and Herzegovina, population-level preventive strategies are essential. Public health initiatives should focus on healthy nutrition, physical activity promotion, obesity prevention, diabetes screening, and awareness campaigns regarding MASLD and cardiometabolic health.

Key Recommendations

1. **Lifestyle intervention remains the foundation of MASLD management**
   Sustained weight reduction of ≥7–10% achieved through dietary modification and regular physical activity is the cornerstone of MASLD treatment and is associated with improvements in hepatic steatosis, necroinflammation, and, in some patients, fibrosis.
2. **Pharmacological therapy should be reserved for patients at increased risk of progression**
   Drug therapy may be considered in patients with significant fibrosis (F ≥2) or high-risk clinical profiles (age >50 years, type 2 diabetes, metabolic syndrome, persistently elevated aminotransferases, or evidence of active inflammation), particularly when lifestyle interventions alone are insufficient.
3. **Optimal management of cardiometabolic comorbidities is mandatory**
   Strict glycaemic control in type 2 diabetes and aggressive lipid-lowering therapy, including statins, are integral components of MASLD care and are essential for reducing long-term cardiovascular morbidity and mortality.
4. **Statins are safe in MASLD and compensated cirrhosis**
   Although not MASLD-specific therapies, statins should not be withheld when clinically indicated for dyslipidaemia or cardiovascular risk prevention, including in patients with compensated cirrhosis.
5. **Selected agents may be used in carefully defined patient subgroups**
   Pioglitazone may be considered in patients with biopsy-proven MASH, while vitamin E can be used in non-diabetic patients without cirrhosis; both require individualized benefit–risk assessment due to potential adverse effects.
6. **UDCA has a favourable safety profile but limited histological efficacy**
   Ursodeoxycholic acid improves liver enzymes and metabolic parameters and appears most useful in early disease stages (F0–F2), although current evidence does not support a consistent histological benefit.
7. **Metformin, GLP-1 receptor agonists, and SGLT2 inhibitors should be used for metabolic indications**
   These agents are not approved as MASLD-specific therapies but may confer indirect hepatic benefits through weight loss, improved insulin sensitivity, and cardiometabolic risk reduction when prescribed for diabetes or obesity.
8. **Bile acids are key regulators in MASLD pathophysiology**
   Alterations in bile acid composition and signaling via FXR-, TGR5-, and FGF19-mediated pathways play a central role in lipid metabolism, glucose homeostasis, inflammation, and fibrosis progression, and correlate with disease severity.
9. **Bile acid–targeting therapies represent an important future direction**
   Pharmacological modulation of bile acid signaling (e.g., FXR agonists, TGR5 agonists, FGF19 analogues, nor-UDCA) shows promise for improving steatosis, inflammation, and fibrosis, but current evidence remains insufficient for routine clinical use.
10. **Advanced and obesity-directed interventions should be individualized and centralized**
    Resmetirom may be considered in non-cirrhotic patients with F ≥2 fibrosis, while endoscopic

bariatric procedures, bariatric surgery, and liver transplantation are reserved for selected patients and should be managed within secondary and tertiary healthcare settings through a multidisciplinary approach.

Evidence Gaps and Research Priorities

Despite the growing burden of MASLD, significant evidence gaps remain in BiH. Currently, no population-based epidemiological studies are available to accurately define the prevalence, incidence, fibrosis burden, or long-term outcomes of MASLD in the country. Consequently, most recommendations presented in this guideline are based on international evidence adapted to the local healthcare setting. Future research efforts should prioritize the establishment of national epidemiological data, including studies assessing disease prevalence in the general population and in high-risk groups such as individuals with obesity, type 2 diabetes, and metabolic syndrome. Additional priorities include evaluation of the diagnostic performance and cost-effectiveness of non-invasive fibrosis assessment strategies in routine clinical practice, assessment of referral pathways across different levels of healthcare, and characterization of liver-related and cardiovascular outcomes among patients with MASLD.

In addition to epidemiological and clinical research, implementation research should be encouraged to evaluate the effectiveness of integrated care pathways across primary, secondary, and tertiary healthcare, the feasibility of structured lifestyle intervention programmes, and the impact of public health strategies aimed at improving awareness, early detection, and prevention of MASLD. Such studies would support optimization of healthcare delivery and facilitate future refinement of national recommendations. The development of national registries and multicentre collaborative studies would provide valuable information regarding disease burden, healthcare resource utilization, and treatment outcomes. Such data are essential for future updates of these guidelines and for informing healthcare policy, resource allocation, and public health strategies aimed at reducing the growing impact of MASLD in BA.

Conclusion

MASLD is one of the most prevalent chronic liver diseases and represents a major public health challenge in Bosnia and Herzegovina. MASLD should not be regarded as an isolated liver condition but rather as the hepatic manifestation of systemic metabolic dysfunction, closely linked to type 2 diabetes, obesity, dyslipidemia, and cardiovascular disease, which together determine overall morbidity and mortality.

The stage of liver fibrosis is the strongest predictor of liver-related outcomes in MASLD. Consequently, early identification of patients at risk, appropriate risk stratification, and timely referral of individuals with advanced fibrosis are central elements of effective disease management. The use of validated non-invasive tests—particularly the FIB-4 index as a first-line tool in primary care, followed by selective application of elastography—enables accurate, safe, and resource-efficient assessment while minimizing the need for invasive diagnostic procedures.

Primary care plays a pivotal role in the management of MASLD, including early detection, long-term follow-up of low-risk patients, and optimization of cardiometabolic comorbidities. Clearly defined referral pathways allow timely specialist involvement for patients with suspected advanced fibrosis or cirrhosis, ensuring appropriate surveillance for hepatocellular carcinoma and management of liver-related complications.

Currently, no pharmacological therapy is approved exclusively for MASLD; therefore, lifestyle modification, sustained weight reduction, and optimal treatment of associated metabolic disorders remain the cornerstone of therapy. An integrated, multidisciplinary approach involving family physicians, endocrinologists, cardiologists, and hepatologists is essential to improve clinical outcomes and reduce the long-term burden of MASLD on the healthcare system. The implementation of this guideline aims to standardize clinical practice

across BiH, promote early diagnosis, support rational use of healthcare resources, and ultimately reduce MASLD-related complications while improving quality of life and long-term outcomes for affected patients.

What Is Already Known on This Topic

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disease globally and a major driver of liver- and cardiovascular-related morbidity and mortality. Disease severity and long-term outcomes are primarily determined by the stage of liver fibrosis. International guidelines emphasize lifestyle modification, management of cardiometabolic comorbidities, non-invasive fibrosis risk stratification, and surveillance for hepatocellular carcinoma in advanced disease. However, translating these recommendations into routine clinical practice remains challenging, particularly in healthcare systems with limited resources and fragmented care pathways. Clear delineation of roles across primary, secondary, and tertiary healthcare levels, as well as adaptation of international recommendations to local healthcare structures, is often lacking.

What This Study Adds

These national clinical practice guidelines provide the first country-specific, consensus-based recommendations for the diagnosis, risk stratification, and management of MASLD in Bosnia and Herzegovina. The document adapts international evidence to local healthcare structures and resource availability, emphasizing a stepwise, non-invasive diagnostic approach and the central coordinating role of primary healthcare. By defining clear referral pathways and integrating lifestyle, pharmacological, interventional, and transplant-related strategies, the guidelines aim to standardize MASLD care, improve early detection of advanced fibrosis, and support practical implementation of evidence-based management across all levels of care.

Authors' Contributions: Conception and design: ZE, HA, KM, GT and BDM; Acquisition, analysis and interpretation of data: ZE, HA, KM, GT and BDM; Drafting of the article: ZE, HA, KM, GT and BDM; Revising it critically for important intellectual content: BE, BKZ, BG, ČN, DA, HB, KA, JL, JP, MA, PBN, SD and ZN; Approved final version of the manuscript: all authors.

Conflict of Interest: The authors declare that they have no conflict of interest.

References

1. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024;81(3):492-542. doi: 10.1016/j.jhep.2024.04.031. PMID: 38851997.
2. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023;77(5):1797-835. doi: 10.1097/HEP.0000000000000323. PMID: 36727674.
3. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77(4):1335-47. doi: 10.1097/HEP.0000000000000004. PMID: 36626630.
4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84. doi: 10.1002/hep.28431. PMID: 26707365.
5. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol. 2018;69(4):896-904. doi: 10.1016/j.jhep.2018.05.036. PMID: 29886156.
6. Mantovani A, Zaza G, Byrne CD, Lonardo A, Zoppini G, Bonora E, et al. Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: A systematic review and meta-analysis. Metabolism. 2018;79:64-76. doi: 10.1016/j.metabol.2017.11.003. PMID: 29137912.
7. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017;65(5):1557-65. doi: 10.1002/hep.29085. PMID: 28130788.
8. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015;61(5):1547-54. doi: 10.1002/hep.27368. PMID: 25125077.
9. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. 2020;73(1):202-9. doi: 10.1016/j.jhep.2020.03.039. PMID: 32278004.
10. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018;24(7):908-22. doi: 10.1038/s41591-018-0104-9. PMID: 29967350.
11. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008;40(12):1461-5. doi: 10.1038/ng.257. PMID: 18820647.
12. Lonardo A, Nascimbeni F, Ballestri S, Fairweather D, Win S, Than TA, et al. Sex Differences in Nonalcoholic

Fatty Liver Disease: State of the Art and Identification of Research Gaps. Hepatology. 2019;70(4):1457-69. doi: 10.1002/hep.30626. PMID: 30924946.

13. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol. 2019;71(4):793-801. doi: 10.1016/j.jhep.2019.06.021. PMID: 31279902.
14. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387(10019):679-90. doi: 10.1016/S0140-6736(15)00803-X. PMID: 26608256.
15. da Silva Pereira ENG, Franco RLC, Santos RDCD, Daliry A. Statins and non-alcoholic fatty liver disease: A concise review. Biomed Pharmacother. 2025;183:117805. doi: 10.1016/j.biopha.2024.117805. PMID: 39755024.
16. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-104. doi: 10.1093/eurheartj/ehy339. PMID: 30165516.
17. Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, et al. Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. Gastroenterology. 2015;149(2):379-88; quiz e15-6. doi: 10.1053/j.gastro.2015.04.014. PMID: 25917783.
18. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-57. doi: 10.1002/hep.29367. PMID: 28714183.
19. Paul S, Davis AM. Diagnosis and Management of Nonalcoholic Fatty Liver Disease. JAMA. 2018;320(23):2474-5. doi: 10.1001/jama.2018.17365. PMID: 30476962.
20. Başaranoğlu M, Örmeci N. Nonalcoholic fatty liver disease: diagnosis, pathogenesis, and management. Turk J Gastroenterol. 2014;25(2):127-32. doi: 10.5152/tjg.2014.7675. PMID: 25003670.
21. Younossi ZM, Golabi P, Price JK, Owrangi S, Gundu-Rao N, Satchi R, et al. The Global Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among Patients With Type 2 Diabetes. Clin Gastroenterol Hepatol. 2024;22(10):1999-2010.e8. doi: 10.1016/j.cgh.2024.03.006. PMID: 38521116.
22. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021;75(3):659-89. doi: 10.1016/j.jhep.2021.05.025. PMID: 34166721.
23. van Kleef LA, Sonneveld MJ, de Man RA, de Knegt RJ. Poor performance of FIB-4 in elderly individuals at risk for chronic liver disease - implications for the clinical utility of the EASL NIT guideline. J Hepatol. 2022;76(1):245-6. doi: 10.1016/j.jhep.2021.08.017. PMID: 34461208.
24. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011;54(3):1082-90. doi: 10.1002/hep.24452. PMID: 21618575.
25. Caussy C, Johansson L. Magnetic resonance-based biomarkers in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Endocrinol Diabetes Metab. 2020;3(4):e00134. doi: 10.1002/edm2.134. PMID: 33102797.
26. Singh S, Venkatesh SK, Loomba R, Wang Z, Sirlin C, Chen J, et al. Magnetic resonance elastography for staging liver fibrosis in non-alcoholic fatty liver disease: a diagnostic accuracy systematic review and individual participant data pooled analysis. Eur Radiol. 2016;26(5):1431-40. doi: 10.1007/s00330-015-3949-z. PMID: 26314479.
27. Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan WK, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol. 2020;5(4):362-73. doi: 10.1016/S2468-1253(19)30383-8. PMID: 32027858.
28. Ravaioli F, Dajti E, Mantovani A, Newsome PN, Targher G, Colecchia A. Diagnostic accuracy of FibroScan-AST (FAST) score for the non-invasive identification of patients with fibrotic non-alcoholic steatohepatitis: a systematic review and meta-analysis. Gut. 2023;72(7):1399-409. doi: 10.1136/gutjnl-2022-328689. PMID: 36599683.
29. Natarajan Y, Loomba R. Magnetic Resonance Elastography for the Clinical Risk Assessment of Fibrosis, Cirrhosis, and Portal Hypertension in Patients With NAFLD. J Clin Exp Hepatol. 2022;12(1):174-9. doi: 10.1016/j.jceh.2021.08.002. PMID: 35068797.
30. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846-54. doi: 10.1002/hep.21496. PMID: 17393509.
31. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut. 2010;59(9):1265-9. doi: 10.1136/gut.2010.216077. PMID: 20801772.
32. McPherson S, Anstee QM, Henderson E, Day CP, Burt AD. Are simple noninvasive scoring systems for fibrosis reliable in patients with NAFLD and normal ALT levels? Eur J Gastroenterol Hepatol. 2013;25(6):652-8. doi: 10.1097/MEG.0b013e32835d72cf. PMID: 23325287.
33. Demir M, Lang S, Nierhoff D, Drebber U, Hardt A, Wedemeyer I, et al. Stepwise combination of

simple noninvasive fibrosis scoring systems increases diagnostic accuracy in nonalcoholic fatty liver disease. J Clin Gastroenterol. 2013;47(8):719-26. doi: 10.1097/MCG.0b013e3182819a89. PMID: 23442837.

34. Alkhouri N, Sedki E, Alisi A, Lopez R, Pinzani M, Feldstein AE, et al. Combined pediatric NAFLD fibrosis index and transient elastography to predict clinically significant fibrosis in children with fatty liver disease. Liver Int. 2013;33(1):79-85. doi: 10.1111/liv.12024. PMID: 23146095.
35. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. J Hepatol. 2025;82(2):315-74. doi: 10.1016/j.jhep.2024.08.028. PMID: 39690085.
36. Linero PL, Castilla-Guerra L. Management of Cardiovascular Risk in the Non-alcoholic Fatty Liver Disease Setting. Eur Cardiol. 2024;19:e02. doi: 10.15420/ecr.2023.19. PMCID: PMC11131151.
37. Duell PB, Welty FK, Miller M, Chait A, Hammond G, Ahmad Z, et al. Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2022;42(6):e168-85. doi: 10.1161/ATV.0000000000000153. PMID: 35418240.
38. Saavedra R, Ramirez B, Jay B. Strategies to Manage Obesity: Lifestyle. Methodist Debakey Cardiovasc J. 2025;21(2):53-61. doi: 10.14797/mdcvj.1510. PMID: 39990756.
39. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015;149(2):367-78.e5; quiz e14-5. doi: 10.1053/j.gastro.2015.04.005. PMID: 25865049.
40. Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol. 2017;67(4):829-46. doi: 10.1016/j.jhep.2017.05.016. PMID: 28545937.
41. Stavropoulos K, Imprialos K, Pittaras A, Faselis C, Narayan P, Kokkinos P. Lifestyle Modifications in Non-Alcoholic Fatty Liver Disease and Non- Alcoholic Steatohepatitis. Curr Vasc Pharmacol. 2018;16(3):239-45. doi: 10.2174/1570161115666170621080835. PMID: 28637408.
42. Lassailly G, Caiazzo R, Ntandja-Wandji LC, Gnemmi V, Baud G, Verkindt H, et al. Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis. Gastroenterology. 2020;159(4):1290-301.e5. doi: 10.1053/j.gastro.2020.06.006. PMID: 32553765.
43. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med. 2018;378(25):e34. doi: 10.1056/NEJMoa1800389. PMID: 29897866.
44. Nseir W, Hellou E, Assy N. Role of diet and lifestyle changes in nonalcoholic fatty liver disease. World J Gastroenterol. 2014;20(28):9338-44. doi: 10.3748/wjg.v20.i28.9338. PMID: 25071328.
45. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol. 2012;57(1):157-66. doi: 10.1016/j.jhep.2012.02.023. PMID: 22414768.
46. Hallsworth K, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. Gut. 2011;60(9):1278-83. doi: 10.1136/gut.2011.242073. PMID: 21708823.
47. Johnson NA, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. Hepatology. 2009;50(4):1105-12. doi: 10.1002/hep.23129. PMID: 19637289.
48. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ. 2017;359:j5024. doi: 10.1136/bmj.j5024. PMID: 29167102.
49. Kennedy OJ, Roderick P, Poole R, Parkes J. Coffee, caffeine and non-alcoholic fatty liver disease? Therap Adv Gastroenterol. 2016;9(3):417-8. doi: 10.1177/1756283X16636765. PMID: 27134669.
50. Jung HS, Chang Y, Kwon MJ, Sung E, Yun KE, Cho YK, et al. Smoking and the Risk of Non-Alcoholic Fatty Liver Disease: A Cohort Study. Am J Gastroenterol. 2019;114(3):453-63. doi: 10.1038/s41395-018-0283-5. PMID: 30353055.
51. Kim NH, Jung YS, Hong HP, Park JH, Kim HJ, Park DI, et al. Association between cotinine-verified smoking status and risk of nonalcoholic fatty liver disease. Liver Int. 2018;38(8):1487-94. doi: 10.1111/liv.13701. PMID: 29359396.
52. Kasper P, Martin A, Lang S, Kütting F, Goeser T, Demir M, et al. NAFLD and cardiovascular diseases: a clinical review. Clin Res Cardiol. 2021;110(7):921-37. doi: 10.1007/s00392-020-01709-7. PMID: 32696080.
53. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet. 2010;376(9756):1916-22. doi: 10.1016/S0140-6736(10)61272-X. PMID: 21109302.
54. Alkasabrah O, Joshi DK, Hafeez A, Agrawal SP, Frishman WH, Aronow WS. Statins and the Cardio-Hepatic Axis: Balancing Cardiovascular Protection with Liver Disease Safety. Cardiol Rev. 2025 Nov 8. doi: 10.1097/CRD.0000000000001122. PMID: 41204625.
55. Abdulrazzak E, Fakhoury B, Jaan A, Ebrahim M, Alabdul Razzak I, Shehadah A, et al. Statin Therapy and Portal

Pressure Reduction in Cirrhosis: A Systematic Review and Meta-Analysis. Liver Int. 2025;45(10):e70326. doi: 10.1111/liv.70326. PMID: 40891266.

56. Haukeland JW, Konopski Z, Eggesbø HB, von Volkmann HL, Raschpichler G, Bjøro K, et al. Metformin in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. Scand J Gastroenterol. 2009;44(7):853-60. doi: 10.1080/00365520902845268. PMID: 19811343.
57. Rouabhia S, Milic N, Abenavoli L. Metformin in the treatment of non-alcoholic fatty liver disease: safety, efficacy and mechanism. Expert Rev Gastroenterol Hepatol. 2014;8(4):343-9. doi: 10.1586/17474124.2014.894880. PMID: 24580044.
58. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med. 2021;384(12):1113-24. doi: 10.1056/NEJMoa2028395. PMID: 33185364.
59. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387(10019):679-90. doi: 10.1016/S0140-6736(15)00803-X. PMID: 26608256.
60. Borodavkin P, Sheridan W, Coelho C, Oštarijaš E, Zaïr ZM, Miras AD, et al. Effects of glucagon-like peptide-1 receptor agonists on histopathological and secondary biomarkers of non-alcoholic steatohepatitis: A systematic review and meta-analysis. Diabetes Obes Metab. 2022;24(2):337-42. doi: 10.1111/dom.14565. PMID: 34605124.
61. Kuchay MS, Krishan S, Mishra SK, Farooqui KJ, Singh MK, Wasir JS, et al. Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial). Diabetes Care. 2018;41(8):1801-8. doi: 10.2337/dc18-0165. PMID: 29895557.
62. Sattar N, Fitchett D, Hantel S, George JT, Zinman B. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial. Diabetologia. 2018;61(10):2155-63. doi: 10.1007/s00125-018-4702-3. PMID: 30066148.
63. Hofmann AF, Hagey LR. Bile acids: chemistry, pathochemistry, biology, pathobiology, and therapeutics. Cell Mol Life Sci. 2008;65:2461-83. doi: 10.1007/s00018-008-7568-6. PMID: 18488143.
64. Amaral JD, Viana RJ, Ramalho RM, Steer CJ, Rodrigues CM. Bile acids: regulation of apoptosis by ursodeoxycholic acid. J Lipid Res. 2009;50:1721-34. doi: 10.1194/jlr.R900011-JLR200. PMID: 19417220.
65. Zerem E, Kunosic S, Kurtcehajic A, Zerem D, Zerem O. Bile acids in metabolic dysfunction-associated steatotic liver disease. World J Hepatol. 2025;17(8):108606. doi: 10.4254/wjh.v17.i8.108606. PMID: 40901599.
66. Simental-Mendía M, Sánchez-García A, Simental-Mendía LE. Effect of ursodeoxycholic acid on liver markers: A systematic review and meta-analysis of randomized placebo-controlled clinical trials. Br J Clin Pharmacol. 2020;86:1476-88. doi: 10.1111/bcp.14311. PMID: 32285958.
67. Lin X, Mai M, He T, Huang H, Zhang P, Xia E, et al. Efficiency of ursodeoxycholic acid for the treatment of nonalcoholic steatohepatitis: A systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol. 2022;16:537-45. doi: 10.1080/17474124.2022.2083605. PMID: 35617696.
68. Ratziu V, de Ledinghen V, Oberti F, Mathurin P, Wartelle-Bladou C, Renou C, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. J Hepatol. 2011;54:1011-9. doi: 10.1016/j.jhep.2010.08.030. PMID: 21145828.
69. Zhang W, Tang Y, Huang J, Hu H. Efficacy of ursodeoxycholic acid in nonalcoholic fatty liver disease: An updated meta-analysis of randomized controlled trials. Asia Pac J Clin Nutr. 2020;29(4):696-705. doi: 10.6133/apjcn.202012_29(4).0004. PMID: 33377363.
70. Leuschner UF, Lindenthal B, Herrmann G, Arnold JC, Rössle M, Cordes HJ, et al. High-dose ursodeoxycholic acid therapy for nonalcoholic steatohepatitis: a double-blind, randomized, placebo-controlled trial. Hepatology. 2010;52(2):472-9. doi: 10.1002/hep.23727. PMID: 20683947.
71. Neuman MG, Malnick S, Chertin L. Gamma glutamyl transferase - an underestimated marker for cardiovascular disease and the metabolic syndrome. J Pharm Pharm Sci. 2020;23(1):65-74. doi: 10.18433/jpps30923. PMID: 32310756.
72. Zhao Y, Xin X, Luo XP. The relationship between the ratio of gamma-glutamyltransferase to high-density lipoprotein cholesterol and the risk of diabetes mellitus using publicly available data: a secondary analysis based on a longitudinal study in Japan. Lipids Health Dis. 2023;22(1):7. doi: 10.1186/s12944-023-01772-9. PMID: 36650520.
73. Nadinskaia M, Maevskaya M, Ivashkin V, Kodzoeva K, Pirogova I, Chesnokov E, et al. Ursodeoxycholic acid as a means of preventing atherosclerosis, steatosis and liver fibrosis in patients with nonalcoholic fatty liver disease. World J Gastroenterol. 2021;27(10):959-75. doi: 10.3748/wjg.v27.i10.959. PMID: 33776366.
74. Ko WK, Lee SH, Kim SJ, Jo MJ, Kumar H, Han IB, et al. Anti-inflammatory effects of ursodeoxycholic acid by lipopolysaccharide-stimulated inflammatory responses in RAW 264.7 macrophages. PLoS One. 2017;12(6):e0180673. doi: 10.1371/journal.pone.0180673. PMID: 28665991.
75. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362(18):1675-85. doi: 10.1056/NEJMoa0907929. PMID: 20427778.

76. Juraschek SP, Col H, Ferro K, Turkson-Ocran RN, Cluett JL, Davis RB, et al. DASH-Patterned Groceries and Effects on Blood Pressure: The GoFresh Randomized Clinical Trial. JAMA. 2026;335(1):36-48. doi: 10.1001/jama.2025.21112. PMID: 41206973.
77. Pietu F, Guillaud O, Walter T, Vallin M, Hervieu V, Scoazec JY, et al. Ursodeoxycholic acid with vitamin E in patients with nonalcoholic steatohepatitis: long-term results. Clin Res Hepatol Gastroenterol. 2012;36(2):146-55. doi: 10.1016/j.clinre.2011.10.011. PMID: 22154224.
78. Dufour JF, Oneta CM, Gonvers JJ, Bihl F, Cerny A, Cereda JM, et al. Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin e in nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2006;4(12):1537-43. doi: 10.1016/j.cgh.2006.09.025. PMID: 17162245.
79. Ersöz G, Günşar F, Karasu Z, Akay S, Batur Y, Akarca US. Management of fatty liver disease with vitamin E and C compared to ursodeoxycholic acid treatment. Turk J Gastroenterol. 2005;16(3):124-8. PMID: 16245220.
80. Barchetta I, Angelico F, Del Ben M, Baroni MG, Pozzilli P, Morini S, et al. Strong association between nonalcoholic fatty liver disease (NAFLD) and low 25(OH) vitamin D levels in an adult population with normal serum liver enzymes. BMC Med. 2011;9:85. doi: 10.1186/1741-7015-9-85. PMID: 21749681.
81. Kitson MT, Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. J Hepatol. 2012;57(4):897-909. doi: 10.1016/j.jhep.2012.04.033. PMID: 22634121.
82. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med. 2024;390(6):497-509. doi: 10.1056/NEJMoa2309000. PMID: 38324483.
83. Hashim HT, Alhatemi AQM, Riaz S, Al-Ghuraibawi MA, Alabide AS, Saeed H, et al. Unveiling Resmetirom: A systematic review and meta-analysis on its impact on liver function and safety in non-alcoholic steatohepatitis treatment. JGH Open. 2024;8(10):e70025. doi: 10.1002/jgh3.70025. PMID: 39359614.
84. Raja A, Subhash Sagar R, Saeed S, Zia Ul Haq A, Khan O, Dileep Bhimani P, et al. Safety and efficacy of resmetirom in the treatment of patients with non-alcoholic steatohepatitis and liver fibrosis: a systematic review and meta-analysis. Ann Med Surg (Lond). 2024;86(7):4130-8. doi: 10.1097/MS9.0000000000002195. PMID: 38989228.
85. Knezović E, Hefer M, Blažanović S, Petrović A, Tomičić V, Srb N, et al. Drug Pipeline for MASLD: What Can Be Learned from the Successful Story of Resmetirom. Curr Issues Mol Biol. 2025;47(3):154. doi: 10.3390/cimb47030154. PMID: 40136408.
86. Au K, Zheng MH, Lee WJ, Ghanem OM, Mahawar K, Shabbir A, et al. Resmetirom and Metabolic Dysfunction-Associated Steatohepatitis: Perspectives on Multidisciplinary Management from Global Healthcare Professionals. Curr Obes Rep. 2024;13(4):818-30. doi: 10.1007/s13679-024-00582-z. PMID: 39110384.
87. Wahlström A, Sayin SI, Marschall HU, Bäckhed F. Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism. Cell Metab. 2016;24:41-50. doi: 10.1016/j.cmet.2016.05.005. PMID: 27320064.
88. Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: from UDCA to FXR, PXR and beyond. J Hepatol. 2015;62: S25-S37. doi: 10.1016/j.jhep.2015.02.023. PMID: 25920087.
89. Wang J, Gao J, Zhang Q, Lu J, Yang Y, Cai X, et al. Ileal FXR Knockdown Ameliorates MASLD Progression in Rats via Modulating Bile Acid Metabolism Mediated by Gut Microbiota. J Gastroenterol Hepatol. 2025;40(8):2091-103. doi: 10.1111/jgh.17017. PMID: 40411313.
90. Rodrigues CM, Steer CJ. The therapeutic effects of ursodeoxycholic acid as an anti-apoptotic agent. Expert Opin Investig Drugs. 2001;10:1243-53. doi: 10.1517/13543784.10.7.1243. PMID: 11772248.
91. Sanyal AJ, Ratziu V, Loomba R, Anstee QM, Kowdley KV, Rinella ME, et al. Results from a new efficacy and safety analysis of the REGENERATE trial of obeticholic acid for treatment of pre-cirrhotic fibrosis due to non-alcoholic steatohepatitis. J Hepatol. 2023;79:1110-20. doi: 10.1016/j.jhep.2023.07.014. PMID: 37517454.
92. Rinella ME, Dufour JF, Anstee QM, Goodman Z, Younossi Z, Harrison SA, et al. Non-invasive evaluation of response to obeticholic acid in patients with NASH: Results from the REGENERATE study. J Hepatol. 2022;76:536-48. doi: 10.1016/j.jhep.2021.10.029. PMID: 34793868.
93. Wang W, Zhao J, Gui W, Sun D, Dai H, Xiao L, et al. Tauroursodeoxycholic acid inhibits intestinal inflammation and barrier disruption in mice with non-alcoholic fatty liver disease. Br J Pharmacol. 2018;175:469-84. doi: 10.1111/bph.14095. PMID: 29139555.
94. Lu Q, Jiang Z, Wang Q, Hu H, Zhao G. The effect of Tauroursodeoxycholic acid (TUDCA) and gut microbiota on murine gallbladder stone formation. Ann Hepatol. 2021;23:100289. doi: 10.1016/j.aohep.2020.100289. PMID: 33217585.
95. Patel K, Harrison SA, Elkhashab M, Trotter JF, Herring R, Rojter SE, et al. Cilofexor, a Nonsteroidal FXR Agonist, in Patients With Noncirrhotic NASH: A Phase 2 Randomized Controlled Trial. Hepatology. 2020;72:58-71. doi: 10.1002/hep.31205. PMID: 32115759.
96. Alkhouri N, Herring R, Kabler H, Kayali Z, Hassanein T, Kohli A, et al. Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: A randomised, open-label phase II trial. J Hepatol. 2022;77:607-18. doi: 10.1016/j.jhep.2022.04.003. PMID: 35439567.
97. Traussnigg S, Schattenberg JM, Demir M, Wiegand J, Geier A, Teuber G, et al. Norursodeoxycholic acid versus placebo in the treatment of non-alcoholic fatty liver disease: a double-blind, randomised, placebo-controlled,

phase 2 dose-finding trial. Lancet Gastroenterol Hepatol. 2019;4:781-93. doi: 10.1016/S2468-1253(19)30184-0. PMID: 31345778.

98. Carlsson B, Lindén D, Brolén G, Liljeblad M, Bjursell M, Romeo S, et al. Review article: the emerging role of genetics in precision medicine for patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2020;51:1305-20. doi: 10.1111/apt.15738. PMID: 32383295.
99. Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med. 2025;392(21):2089-99. doi: 10.1056/NEJMoa2413258. PMID: 40305708.
100. Alkhouri N. Recent Data from the ESSENCE Trial on Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. Gastroenterol Hepatol (N Y). 2025;21(2):133-5. PMID: 40115605.
101. Luo S, Liu H, Jin W. Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med. 2025;393(8):826. doi: 10.1056/NEJMc2509454. PMID: 40834308.
102. Kim Y, Zeng N, Winer-Jones JP, Bonafede M, Lobo F, O'Donnell J, et al. Retrospective Study of Real-World Treatment Patterns of Subcutaneous Semaglutide Use Among Patients with Metabolic Dysfunction-Associated Steatohepatitis in the United States. Clinicoecon Outcomes Res. 2025; 17:743-54. doi: 10.2147/CEOR.S546841. PMID: 41147033.
103. Fiorucci S, Urbani G. Tirzepatide for metabolic dysfunction-associated steatohepatitis: results from phase II clinical trials and perspectives. Expert Opin Investig Drugs. 2025;34(9):655-63. doi: 10.1080/13543784.2025.2546812. PMID: 40782123.
104. Arai T, Atsukawa M, Nagao C, Yamada Z, Rokugo T, Suzuki K, et al. Effect of Tirzepatide Treatment on Hepatic Biomarkers in Patients With Metabolic Dysfunction-Associated Steatotic Liver Disease and Type 2 Diabetes Mellitus. Hepatol Res. 2025;55(10):1346-52. doi: 10.1111/hepr.14241. PMID: 40616360.
105. Li Y, Sun W, Liu H, Ruan XZ. Tirzepatide, a dual GIP/GLP-1 receptor agonist, alleviates metabolic dysfunction-associated steatotic liver disease by reducing the expression of CD36 and OBP2A. Genes Dis. 2025;12(6):101761. doi: 10.1016/j.gendis.2025.101761. PMID: 40837406.
106. Reja D, Zhang C, Sarkar A. Endoscopic bariatrics: current therapies and future directions. Transl Gastroenterol Hepatol. 2022;7:21. doi: 10.21037/tgh.2020.03.09. PMID: 35548475.
107. Moutzoukis MK, Argyriou K, Manolakis A, Kapsoritakis A, Christodoulou D. Endoscopic bariatrics: Current status and emerging technologies. World J Gastrointest Endosc 2025;17(10):109031. doi: 10.4253/wjge.v17.i10.109031. PMID: 41181529.
108. Mingrone G, Rajagopalan H. Bariatrics and endoscopic therapies for the treatment of metabolic disease: Past, present, and future. Diabetes Res Clin Pract. 2024;211:111651. doi: 10.1016/j.diabres.2024.111651. PMID: 38580037.
109. Younossi ZM, Stepanova M, Ong J, Trimble G, AlQahtani S, Younossi I, et al. Nonalcoholic Steatohepatitis Is the Most Rapidly Increasing Indication for Liver Transplantation in the United States. Clin Gastroenterol Hepatol. 2021; 19(3):580-9.e5. doi: 10.1016/j.cgh.2020.05.064. PMID: 32531342.
110. Lim TY, Steggerda JA, Trivedi H, Luu M, Vipani A, Adjei MA, et al. Outcomes from Referral to Transplant for Patients with MASLD: A California Liver Network Study. J Clin Med. 2025;14(21):7841. doi: 10.3390/jcm14217841. PMID: 41227237.
111. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018;154(6):1706-18.e1. doi: 10.1053/j.gastro.2018.01.064. PMID: 29425931.
112. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76(3):681-93. doi: 10.1016/j.jhep.2021.11.018. PMID: 34801630.