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Expert consensus on improving clinical approaches to managing liver diseases in patients with comorbidities

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Non-alcoholic fatty liver disease affects up to 38% of the adult population worldwide, making it the most common chronic liver disease. It is a multisystem pathology, which is caused by systemic insulin resistance and related metabolic dysfunction, and lead to steatosis, steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma, as well as to extrahepatic complications such as cardiovascular diseases, type 2 diabetes mellitus and chronic kidney disease.
In 2023 the main international liver study associations have proposed to replace the term "non-alcoholic fatty liver disease" with "metabolic associated fatty liver disease" (MAFLD) to better reflect the metabolic origin of the disease. This change in terminology sparked greater scientific interest and a reassessment of clinical strategies.
In March 2024, an Expert Forum on "Clinical Improvement of Approaches to Treating Liver Diseases in Comorbid Patients" brought together 16 key expert specialists of different specialities from Ukraine, Kazakhstan, Uzbekistan, Kyrgyzstan, Georgia, and Armenia. The forum focused on optimizing the treatment of MAFLD in patients with comorbid diseases.
The consensus was adopted on the main recommendations: early diagnosis using modern imaging methods; lifestyle modification (diet and physical activity); pharmacotherapy; in some cases, bariatric surgery. Special attention was paid to the treatment of comorbidities, hepatogenic fatigue with ademetionine and the use of the Charlson index for survival prognosis. The document emphasizes the importance of a multidisciplinary approach, the need for further studies of pathogenesis and the development of targeted therapy. Implementation of these recommendations may improve the quality of life and long-term outcomes for patients with chronic liver disease.
***Conclusions*. MAFLD is characterized by the accumulation of fat in the liver due to metabolic disorders. It is a common disease worldwide. Early diagnosis of the disease is vital because it can progress to severe and terminal conditions (steatohepatitis, cirrhosis, and liver cancer). Therapeutic strategies include: lifestyle changes, pharmacotherapy, and bariatric surgery. Further studies are needed to improve the understanding of the pathogenesis of MAFLD, identify biomarkers of this disease, and develop new therapeutic strategies.**
Keywords: *chronic liver diseases, metabolic-associated fatty liver disease, non-alcoholic fatty liver disease, metabolic syndrome, insulin resistance, expert recommendations, fatigue, comorbid conditions, multidisciplinary approach.*

Експертний консенсус щодо вдосконалення клінічних підходів до тактики ведення захворювань печінки у пацієнтів із супутніми патологіями

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Неалкогольна жирова хвороба печінки уражує до 38% дорослого населення світу, що робить її найпоширенішим хронічним захворюванням печінки. Це мультисистемне захворювання, зумовлене інсулінорезистентністю та метаболічною дисфункцією, що призводить до стеатозу, стеатогепатиту, фіброзу, цирозу та гепатоцелюлярної карциноми, а також до позапечінкових ускладнень, як-от серцево-судинних захворювань, цукрового діабету 2-го типу та хронічної хвороби нирок.

У 2023 р. основні міжнародні асоціації з лікування печінки рекомендували замінити термін «неалкогольна жирова хвороба печінки» на «метаболічно-асоційована стеатотична хвороба печінки» (МАСХП), щоб краще відобразити метаболічне походження захворювання. Ця зміна викликала новий науковий інтерес та переоцінку клінічних стратегій.

У березні 2024 р. експертний форум із теми «Клінічне вдосконалення підходів до лікування захворювань печінки у коморбідних пацієнтів» зібрав 16 провідних спеціалістів різних спеціальностей з України, Казахстану, Узбекистану, Киргизстану, Грузії та Вірменії. Форум був зосереджений на оптимізації лікування МАСХП у пацієнтів із супутніми захворюваннями. Було досягнуто консенсусу щодо основних рекомендацій: рання діагностика з використанням сучасних методів візуалізації; модифікація способу життя (дієта та фізична активність); фармакотерапія; в окремих випадках – баріатрична хірургія. Особливу увагу приділено лікуванню супутніх захворювань, гепатогенної втомлюваності за допомогою адеметіоніну та застосуванню індексу Чарлсона для прогнозу виживаності.

У документі наголошується на важливості мультидисциплінарного підходу, необхідності подальших досліджень патогенезу й розробки цільової терапії. Впровадження цих рекомендацій може покращити якість життя та довгострокові результати для пацієнтів із хронічними захворюваннями печінки.

Висновки. МАСХП характеризується накопиченням жиру в печінці внаслідок порушення метаболізму і є поширеним захворюванням у всьому світі. Раннє виявлення захворювання є життєво важливим, оскільки воно може прогресувати до тяжких і термінальних станів (стеатогепатит, цироз та рак печінки). Терапевтичні стратегії включають: зміну способу життя, фармакотерапію й баріатричну хірургію. Необхідні подальші дослідження для покращення розуміння патогенезу МАСХП, виявлення біомаркерів цього захворювання та розробки нових терапевтичних стратегій.

Ключові слова: *хронічні захворювання печінки, метаболічно-асоційована стеатотична хвороба печінки, неалкогольна жирова хвороба печінки, метаболічний синдром, інсулінорезистентність, рекомендації експертів, втомлюваність, супутні захворювання, мультидисциплінарний підхід.*

Chronic liver diseases (CLD) is a major cause of mortality and morbidity across the world [1, 2]. Additionally, CLD is associated with an increased risk of cardiovascular disease, which is the primary cause of death among patients with liver conditions [3].

The main phenotypes of CLD include metabolic dysfunction-associated steatotic liver disease (MASLD), drug-induced liver injury, alcohol-related liver disease, and viral hepatitis [2].

Metabolic dysfunction-associated steatotic liver disease [4]

New nomenclature of steatotic liver disease

Recommendation 1. It is important to adopt a new terminology at all levels of healthcare. The terms "metabolic dysfunction-associated steatotic liver disease" (MASLD) and "metabolic dysfunction-associated steatohepatitis" (MASH) should replace "non-alcoholic fatty liver disease" (NAFLD) and "non-alcoholic steatohepatitis" (NASH), respectively.

Diagnosis of MASLD

Recommendation 2. In primary care, the presence of prediabetes, type 2 diabetes mellitus (T2DM), obesity, and/or metabolic syndrome, along with elevated transaminase levels, should raise suspicion for MASLD. Patients in this group require further evaluation for MASLD.

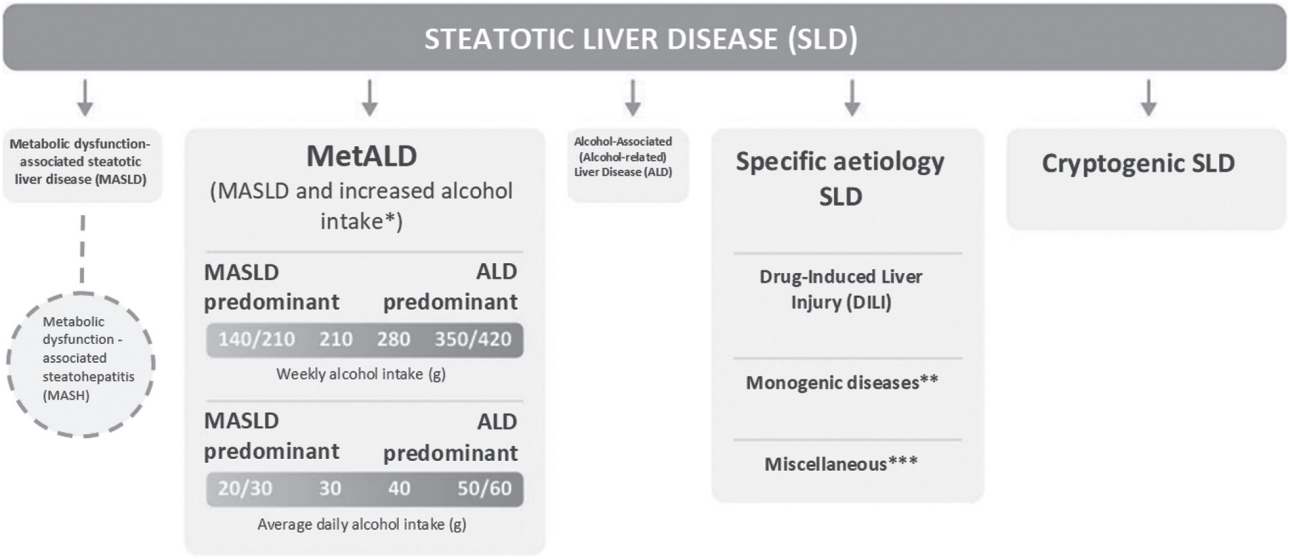
Clinical syndromes and laboratory parameters that assess liver function are detailed in App. 1 [5].

Recommendation 3. The presence of hepatic steatosis, along with at least one of the following cardiometabolic criteria, should be used to diagnose MASLD in adults:

- body mass index (BMI) ≥ 25 kg/m^2 (≥ 23 kg/m^2 in Asian individuals) or waist circumference > 94 cm in men and > 80 cm in women;
- fasting serum glucose ≥ 5.6 mmol/L, 2 hour post-load glucose levels of ≥ 7.8 mmol/L, or glycated haemoglobin (*HbA1c*) ≥ 5.7%, or diagnosed T2DM or treatment for T2DM;
- blood pressure ≥ 130/85 mmHg or the use of specific antihypertensive drug treatment;
- plasma triglycerides ≥ 1.7 mmol/L or the use of lipid-lowering treatment;
- plasma high-density lipoprotein (HDL) cholesterol ≤ 1.0 mmol/L in men, ≤ 1.3 mmol/L in women, or the use of lipid-lowering treatments.

Recommendation 4. Diagnostic imaging techniques like ultrasound, steatometry, computed tomography (CT), and magnetic resonance imaging (MRI) should be employed to detect hepatic steatosis, with magnetic resonance spectroscopy (MRS) being the preferred method for measuring liver fat content.

Recommendation 5. The criterion for diagnosing metabolic and alcohol-associated liver disease (MetALD) is weekly alcohol intake of 140–350 g for women, 210–420 g in males (average daily 20–50 g for women, 30–60 g for men). MASLD predominates with weekly



Steatotic liver disease (SLD) subclassification [4]

Notes: * – Weekly intake: 140–350 g female, 210–420 g male (average daily 20–50 g female, 30–60 g male);
** – e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism;
*** – e.g. Hepatitis C virus (HCV), malnutrition, celiac disease.

alcohol intake under 140 g for women and 210 g for men. Conversely, ALD is predominant in cases of weekly alcohol intake exceeding 350 g/kg for women and 420 g/kg for men.

If other causes of steatosis are identified, the condition is considered to have a combined aetiology.

Recommendation 6. Patients with CLD should be evaluated for the severity of comorbidities using the Charlson Comorbidity Index to predict 10-year survival [6] (App. 2).

MASLD treatment

Recommendation 7. Patients diagnosed with MASLD should be managed by a multidisciplinary team including general practitioners (GPs), internists, gastroenterologists, hepatologists, endocrinologists, cardiologists, rehabilitation specialists, dieticians, and psychologists. MASLD treatment should focus not only on preventing the progression of liver disease but also on managing metabolic risk factors.

Recommendation 8. The most effective strategy for treating MASLD is weight reduction. A weight loss of at least 5% from baseline is recommended for steatosis, 7% for steatohepatitis, and 10% for fibrosis. This can be achieved through lifestyle modifications, pharmacotherapy, or, if these are ineffective, bariatric surgery.

Lifestyle modification

Recommendation 9. Weight loss should primarily be achieved through a hypocaloric diet that creates a deficit of 500–1000 kcal per day, combined with at least 45 minutes of moderate-intensity aerobic and anaerobic exercise three times per week.

Recommendation 10. It is essential to limit the intake of fructose, animal proteins, and foods rich in cholesterol and saturated fats while increasing the intake of polyunsaturated fatty acids. The Mediterranean diet has a favourable effect on the course of MASLD [7].

Pharmacotherapy

Recommendation 11. The use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs, liraglutide, semaglutide) is recommended for patients with CLD, especially those with MASLD and MASH who also have T2DM.

Recommendation 12. Administration of vitamin E and pioglitazone may be appropriate for those with MASLD. Pioglitazone is recommended for the treatment of steatohepatitis and/or hepatic fibrosis in individuals with concomitant T2DM, while vitamin E (alpha-tocopherol)* is recommended for patients without T2DM.

Note: * – according to EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) 2024: "Given the lack of robust demonstration of histological efficacy on steatohepatitis and liver fibrosis derived from large phase III trials and potential long-term risks, vitamin E cannot be recommended as a MASH-targeted therapy"[8].

Recommendation 13. Metformin is not recommended for the treatment of MASH, as it only increases insulin sensitivity without improving the liver's histological characteristics. However, metformin may be recommended for patients with MASH who also have T2DM, as it reduces the incidence of hepatocellular carcinoma (HCC).

Recommendation 14. There is evidence that sodium-glucose cotransporter-2 (SGLT-2) inhibitors (empagliflozin, dapagliflozin) can reduce liver fat content and lower the risk of fibrosis, which may have a favourable effect on the progression of MASLD [9–11]. If patients have concomitant T2DM or cardiovascular disease, it is reasonable to consider prescribing medications from this class.

Recommendation 15. The use of ursodeoxycholic acid (UDCA) does not provide significant histological benefits in the treatment of NASH, and further studies are needed to evaluate its efficacy [12–14]. Currently, the approved indication for prescribing UDCA in hepatology is the symptomatic treatment of primary biliary cholangitis [15].

Recommendation 16. Maintaining the homeostasis of ademetionine (S-adenosyl-L-methionine) is essential in MASLD, alcoholic and non-alcoholic cirrhosis, and in chemoprevention courses for hepatocellular carcinoma.

The administration of ademetionine in NAFLD (according to the new nomenclature, MASLD) with intrahepatic cholestasis (IHC) has been shown to help reduce levels of total and conjugated bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase (GGTP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), while also alleviating or eliminating symptoms of intrahepatic cholestasis in adults [16, 17].

Long-term use of ademetionine exhibits a hypolipidemic effect [17], which is particularly significant for patients with concomitant cardiovascular disease.

Bariatric Surgery

Recommendation 17. Bariatric surgery is recommended for individuals with class III obesity (BMI ≥ 40 kg/m^2), class II obesity (BMI 34.9–40 kg/m^2) in combination with at least one obesity-associated comorbidity, or class I obesity combined with T2DM who have not achieved adequate metabolic control through lifestyle modification and pharmacotherapy.

Pathological chronic fatigue (PCF) in liver disease

Hepatogenic fatigue in patients with MASLD negatively affects quality of life and is associated with a 2.3-fold increase in mortality compared to MASLD patients without increased fatigue [18].

Recommendation 18. Since PCF significantly impairs quality of life in patients with CLD, clinicians should prioritize the symptomatic management of this condition.

Diagnosis of PCF

Recommendation 19. Hepatogenic fatigue should be diagnosed using the Fatigue Assessment Scale (FAS) questionnaire [19] (App. 3).

Treatment of PCF

Recommendation 20. Ademetionine is recommended for the treatment of hepatogenic fatigue.

In managing increased fatigue, ademetionine works on two levels. At the liver level, it reduces pathological inflammatory signals in hepatocytes (lowering levels of TNF-α, IL-6, IL-1β) and prevents these signals from reaching the brain. In the brain, ademetionine acts as a methyl group donor, participating in the synthesis of various mediators, primarily serotonin, and improving nerve impulse conduction [20–22].

CONCLUSIONS

MASLD is characterized by fat accumulation in the liver due to metabolic dysregulation and is a prevalent condition worldwide, closely associated with insulin resistance, T2DM and obesity.

Early detection of MASLD through imaging techniques (steatometry, fibroscan, fibrotest), non-invasive methods, or liver biopsy is vital, as this disease can progress to severe and terminal conditions (steatohepatitis, cirrhosis, and liver cancer). Therapeutic strategies for MASLD include lifestyle modifications, pharmacotherapy, and bariatric surgery. Further research is necessary to enhance our understanding of the pathogenesis of MASLD, identify biomarkers for this disease, and develop new therapeutic strategies.

Appendix 1

Clinical syndromes and laboratory indicators that allow assessment of the functional state of the liver

Main clinical syndromes of liver diseases	Pathogenetic mechanism	Diagnostic sign
Cytolysis syndrome	Destruction of hepatocytes (necrosis and dystrophy)	Blood test indicators: ↑ ALT, ↑ AST, ↑ LDH (primarily LDH4 and LDH3), ↑ iron, ↑ ferritin, ↑ bilirubin (both forms)
Cholestasis syndrome	Extracellular: Impaired bile flow leads to stasis in the bile ducts. Intracellular: ultrastructural changes occur in hepatocytes, resulting in the accumulation of bile components within these cells	Jaundice, Pruritus, Xanthomas. Blood test indicators: ↑ Alkaline phosphatase, ↑ Gamma-glutamyltransferase, ↑ Cholesterol, ↑ Bilirubin (primarily the direct form), ↑ Bile acids in blood, ↑ Urobilin in urine, ↓ Stercobilin in faeces
Mesenchymal inflammatory syndrome	Intrahepatic and systemic changes in cellular and humoral immune reaction indicators	Fever, Arthralgia, Lymphadenopathy (swollen lymph nodes). Blood test indicators: ↑ ESR, ↑ C-reactive protein (CRP), ↑ Immunoglobulin levels (IgA, IgM, IgG), ↑ Antibody titres
Liver cell failure syndrome	Decreased detoxification and synthetic functions of hepatocytes	Decrease in body weight, presence of liver-related signs. Blood test indicators: ↓ Total protein, Albumin, Cholesterol Prothrombin index (PTI) and fibrinogen, ↑ Prothrombin time (PT) and international normalized ratio (INR), ↑ Bilirubin (primarily the indirect form)

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Main clinical syndromes of liver diseases	Pathogenetic mechanism	Diagnostic sign
Development of liver fibrosis	Replacement of hepatocytes with scar connective tissue up to the development of liver cirrhosis	↑ Hepatic tissue density (elastometry). Progression of fibrosis stages according to liver biopsy data. In cirrhosis: development of portal hypertension. Blood test indicators: ↑ Serum markers of fibrosis (e.g., hyaluronic acid, propeptide-III-procollagen, etc.)

Appendix 2

Charlson Comorbidity Index

To calculate the Charlson Comorbidity Index, sum the scores for age and medical conditions:

Points	Condition
1	Myocardial infarction. Congestive heart failure. Peripheral arterial disease. Cerebrovascular accident (CVA) or transient ischemic attack (TIA). Dementia. Chronic pulmonary disease. Connective tissue disease. Peptic ulcer disease. Mild liver disease, diabetes mellitus
2	Hemiplegia. Chronic kidney disease, moderate to severe. Diabetes mellitus with end-organ damage. Localized solid tumour. Leukaemia. Lymphoma
3	Moderate to severe CLD
6	Metastatic solid tumour AIDS (disease, not just viraemia)
	+ 1 point is added for every 10 years of age over 40 (e.g., ages 40–49 = 1 point, 50–59 = 2 points, etc.)

Sum of points	10-year survival rate, %
0	99
1	96
2	90
3	77
4	53
5	21

Appendix 3

Fatigue Assessment Scale (FAS)

No.	Question	Never	Sometimes	Regularly	Often	Always
1	I am bothered by fatigue	1	2	3	4	5
2	I get tired very quickly	1	2	3	4	5
3	I don't do much during the day	1	2	3	4	5
4	I have enough energy for everyday life	5	4	3	2	1
5	Physically, I feel exhausted	1	2	3	4	5
6	I have problems to start things	1	2	3	4	5
7	I have problems to think clearly	1	2	3	4	5
8	I feel no desire to do anything	1	2	3	4	5
9	Mentally, I feel exhausted	1	2	3	4	5
10	When I am doing something, I can concentrate quite well	5	4	3	2	1

The FAS is a 10-item questionnaire designed to assess general fatigue: five questions measure mental fatigue, while five others assess physical fatigue. Each question offers 5 response options on a Likert scale (from "never" to "always"). The results are calculated by summing the points, which can range from 10 to 50 points. A higher score indicates a higher degree of fatigue. A score of ≥ 22 points suggests that the patient may have PCF.

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