

## EDITORIAL

## Metabolic Associated Steatotic Liver Disease (MASLD) – Be Aware and Beware


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**Abstract**

Metabolic associated steatotic liver disease (MASLD) is now the most common liver and metabolic disease with rapidly rising prevalence, being among most common causes of liver transplantation, associated with liver mortality, but even more so and earlier in the course of the disease it is underappreciated independent risk factor for cardiovascular (CV) and all-cause mortality. A large body of clinical evidence suggests that MASLD is a multisystem disease whose adverse effects extend far beyond and before the liver gets seriously affected. It has a complex, independent and bidirectional relationship to all MetS components, chronic kidney disease, and CVD, being causal in one and consequential in another patient and that speaks in favor of including liver health assessment in conventional screening of this at-risk population.

Therefore, authors of this editorial call for raising awareness about this condition, write about new nomenclature that better explains what this condition is rather than what it is not, explain how novel simplified positive diagnostic criteria facilitate timely diagnosis and treatment, and offer simple algorithm for evaluation and treatment of liver steatosis in at-risk patients for non hepatologists.

**Keywords:** liver, metabolic syndrome, cardiometabolic risk factors.

*“The good physician treats the disease,  
the great physician treats the patient who has the disease.”*

Sir William Osler

**MASLD – UNDERAPPRECIATED  
INDEPENDENT CARDIOVASCULAR-  
KIDNEY-METABOLIC RISK FACTOR**

Metabolic associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is the most prevalent liver and metabolic disease affecting more than a quarter of global population and outnumbering diabetes mellitus and obesity together (1, 2).

**Epidemiology of MASLD**

MASLD prevalence according to the most recent data is 38%, with 50% increase since the previous analysis (3) and with expected growth. Recent prevalence of MASLD in the overweight and obese population is 70% and 75%, respectively (4), while among patients with type 2 diabetes (T2DM) it is 68.8%, being the highest in Eastern Europe

(80.6%). One should not forget that there is also a lean MASLD (5, 6).

### **MASLD and Cardiovascular-Kidney-Metabolic Factors – “Chicken-and-Egg” Situation**

It is known that human liver has metabolic, nutrient storage and detoxification activities, but also complex immunological activities, all essential to maintain tissue and organ homeostasis that once disrupted lead to dysregulation that is a driver of pathology associated with chronic inflammation (7).

If not recognized or adequately treated, MASLD goes through pathological spectrum of hepatic changes from simple steatosis, steatohepatitis (MASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). This happens in parallel with development of insulin resistance, dysglycemia, atherogenic dyslipidemia, systemic low-grade inflammation, oxidative stress, hypercoagulability, expanded and dysfunctional adipose tissue with visceral adipose tissue deposition, gut dysbiosis, increased activity of renin-angiotensin-aldosterone system, (1), sympathetic nervous system (SNS), dysregulated function of nitric oxide synthase, that are common pathophysiological mechanisms for development of hepatic and extra-hepatic complications. And vice versa – all these pathologic processes contribute to further hepatic injury and fibrosis (8,9).

NAFLD has traditionally been considered a simple liver manifestation of metabolic syndrome (MetS). Today we know that NAFLD, renamed into MASLD, has complex and, more importantly – bidirectional relationship to all MetS components, especially T2DM, hypertension (HTN), chronic kidney disease (CKD), and cardiovascular disease (CVD), independent of other risk-factors (1, 10, 11).

It is important to understand that in constellation of different cardio-kidney-metabolic conditions, MASLD might be causal in one patient, while consequential in the other. It is therefore considered a multisystem disease whose adverse effects extend far beyond

and before the liver gets seriously affected.

### **Complications of MASLD**

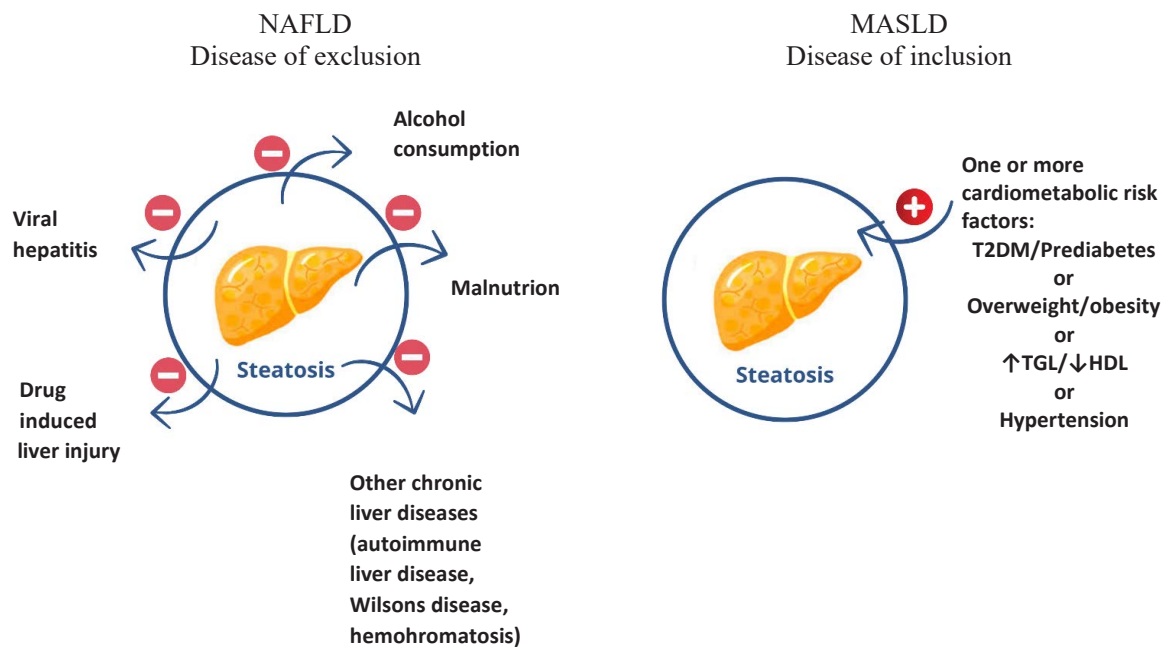
A large body of clinical evidence suggests that MASLD is not at all a benign disease and is associated with liver mortality, being the most common cause of liver transplantation in the United States (US) among those who get listed for HCC, but even more so and earlier in the course of the disease – with the CV and cancer, especially gastrointestinal, and all-cause mortality (12, 11).

Mortality increases exponentially as the fibrosis stage increases, but it is noteworthy that all-cause mortality, unlike liver related mortality, is increasing in MASLD even before stage 1 fibrosis develops.

Due to a plethora of evidence, ESC 2021 put in their guidelines (13) that NAFLD is associated with increased risk of myocardial infarction and stroke, and in 2022 AHA also announced in their scientific statement (14) that NAFLD is a risk factor for development of ASCVD, which is the main cause of death in patients with NAFLD.

It was that same AHA statement where CKD, a previously overlooked but clinically and prognostically important feature of NAFLD and their bidirectional relationship, was also elaborated, with evidence already there and gathered through systematic review and meta-analysis (15). Updated meta-analysis (16) followed, indicating that NAFLD is significantly associated with a ~1.45-fold increased long-term risk of incident CKD stage  $\geq 3$ . It was proved that NAFLD predicts CKD better than FL (fatty liver) or NAFLD (17) and that the risk increases with steatosis severity (18). Causative relationship between NASH and CKD was proved in a murine model (19) that revealed potential pathogenic mechanisms, histological changes that resembled human, together with regression of kidney damage (proteinuria, kidney dysfunction, and fibrosis) following the orthotopic liver transplantation.

It was also in 2022 that the first study investigating bidirectional and independent



**Figure 1: Difference in diagnosis of NAFLD and MASLD.**

NAFLD - Non-alcoholic fatty liver disease, MASLD - Metabolic dysfunction-associated steatotic liver disease, T2DM - Diabetes mellitus typus 2, TGL - Triglycerides, HDL - Highdensity lipoprotein.

relationship between NAFLD and HTN was published (20) proving that NAFLD is associated with a 1.55-fold increased risk of incident HTN, while HTN increases the risk of incident NAFLD by 1.63-fold, and that MASLD was significantly associated with an increase in systolic blood pressure over time compared to no or only FL (21).

Therefore, besides preventing or better control of T2DM, dyslipidemia, and other primarily metabolic conditions by timely recognizing and treating MASLD, it may serve as an important aspect in prevention, slowing or reversing of CVD, CKD and HTA, while control of all those conditions will on the other hand prevent or ameliorate MASLD and liver fibrosis.

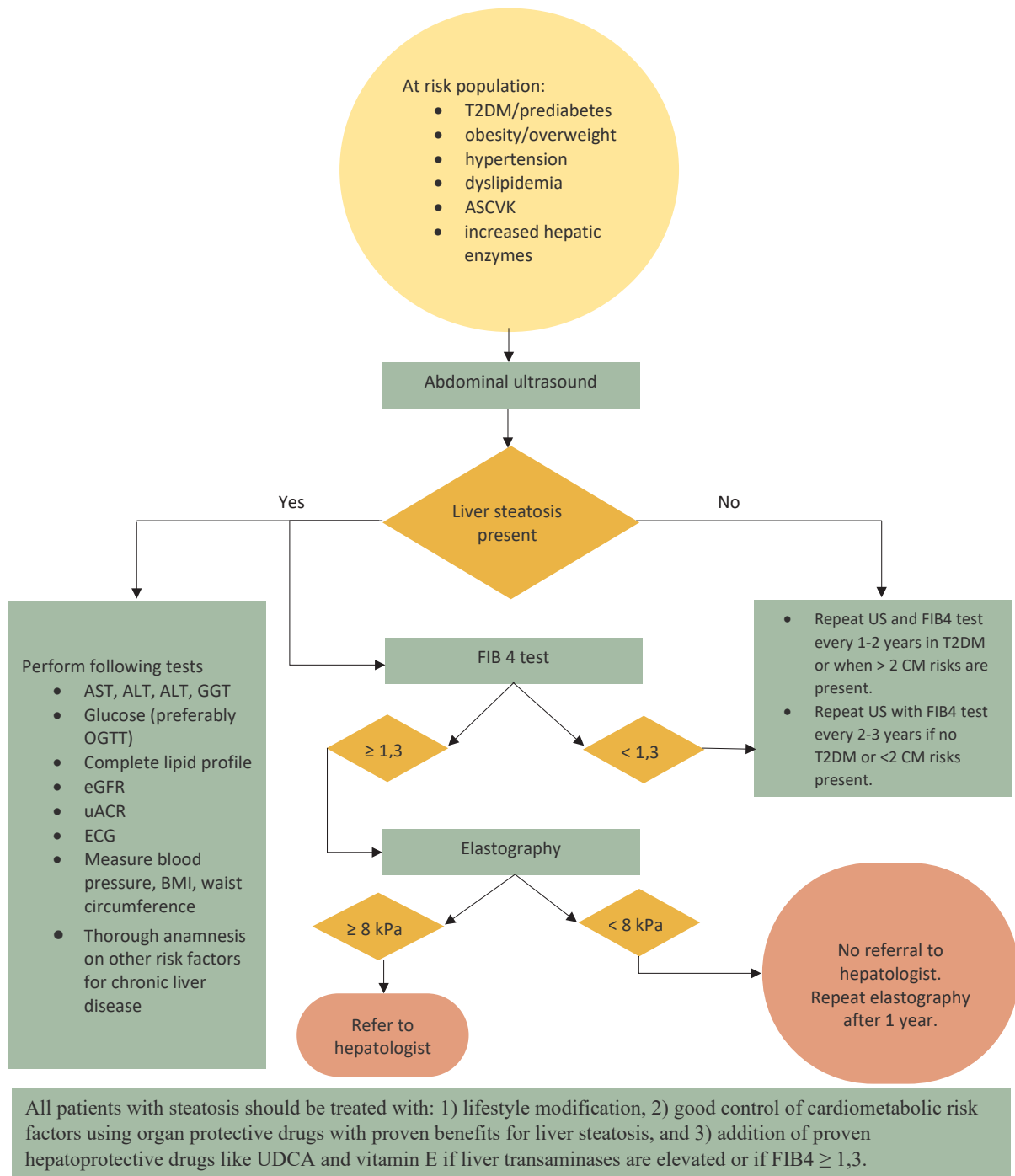
### New Nomenclature and Diagnostic Criteria – Keep Simple and Carry On

It was in 2020 when the term MASLD was proposed to replace NAFLD to better reflect what that condition is rather than what it is not, unrelated to presence or absence of other causes of liver disease (22). Multi-society effort of three large pan-national liver associations, including patient advocates, was put into developing consensus about a

new name to solve problems of exclusionary nature of the previous one, more appropriately describe this disease, and reduce the potential stigma associated with the terminology (23). One of the most significant differences was the removal of exclusion of concurrent liver disease previously required to establish the diagnosis (6, 24), but physicians are encouraged to identify coexistent etiologies of liver injury and treat them in a holistic manner (23) (Figure 1).

It is important to stress that years of work put into research of NAFLD are not in vain for it is proved that 98% of the existing registry cohort of patients with NAFLD would fulfill the new criteria for MASLD (24), the performance of the most commonly used NITs (Noninvasive Tests ) is similar, and MASLD correlates similar (5) or even better than NAFLD (25) with clinical profiles and mortality rates. Therefore, the change in nomenclature was not at all purely semantic.

Important steps that should follow are simple diagnostic algorithms of in-risk populations together with therapeutic options, and authors of this editorial are offering some suggestions (Figure 2). New society guidelines and algorithms are released or upcoming (26, 24,



**Figure 2: Algorithm of evaluation and treatment of liver steatosis in at risk patients or with known liver steatosis for primary care physicians and non hepatologists.**

T2DM Diabetes mellitus typus 2, eGFR Estimated glomerular filtration rate (online calculator, preferably CKD EPI – chronic kidney disease epidemiology collaboration), CM Cardiometabolic, ASCVK Atherosclerotic cardiovascular disease, AST Aspartate aminotransferase, ALT Alanine aminotransferase, GGT Gamma glutamyl transpeptidase, OGTT Glucose tolerance test, uACR Urine albumin-creatinine ratio, ECG electrocardiogram, FIB 4 Fibrosis 4 (online calculator for liver fibrosis), US Ultrasound, UDCA ursodeoxycholic acid.

27), but with all the knowledge we gathered on MASLD, it is important to create guidelines that are not “hepatopetal” but put emphasis on bidirectional relationship of MASLD with its risk-factors and complications for it has important diagnostic and therapeutic implications.

### Therapeutic Directions

Once MASLD is diagnosed, we should try to explain it first as being a cause or a consequence of co-existent conditions. That interplay is often not straight-forward, but one should find the most plausible explanation for

MASLD in each patient in order to treat the patient and not the separate conditions by tailoring therapy individually, avoiding unnecessary polypharmacy, and using modern disease-modifying multi-organ protective therapy. Such drugs that are common denominators of many of these conditions and have proven benefits for treating MASLD are: sodium-glucose transport protein 2 (SGLT2) inhibitors, glucagon-like peptide-1 agonists (GLP-1a), dipeptidyl peptidase 4 (DPP-4) inhibitors, metformin, angiotensin converting enzyme (ACE) inhibitors/ angiotensin receptor blockers (ARBs), statins (28, 29).

The expert opinion is to also introduce proven hepatoprotective drugs such as vitamin E, but more importantly – ursodeoxycholic acid that not only improves liver function, but independently from that also corrects metabolic abnormalities and provides extra-hepatic organ-protection (30-31).

Lifestyle modifications are undoubtedly the cornerstone of therapy while on the other end stands resmetirom as the only MASH-targeted medication recently approved by the Food and Drug Administration in the United States for treating stage 2-3 fibrosis (6) for data suggest benefits of regression of fibrosis even by one stage, and even more profound in later stages (11).

## CONCLUSIONS

MASLD has gone a long way from fatty liver, as it was first described by Thomas Addison in 1800s (32), then nonalcoholic fatty liver (NAFLD) that was being perceived as accidental finding on ultrasound and complicated to diagnose, to the present day when it is being recognized as not only hepatic but even more

so – important independent extra-hepatic, especially CV risk factor. MASLD has received attention in academic circles, but the information was not articulated in parallel to the general healthcare practitioners in whom it is priority to raise awareness. It is much easier now, when academic society recognizes and embraces cardiovascular-kidney-metabolic (CKM) syndrome to include liver health assessment in conventional screening of in-risk population. Diagnosing MASLD by novel simplified positive criteria is practical and simple and this could help first-contact physicians to timely identify and treat this otherwise silent condition which, if left untreated, may cause major extra-hepatic adverse events, long before it causes hepatic ones. Since MASLD has bidirectional relation to its risk factors, being a causal condition to one patient while consequential to the other, there is and will probably not be single solution or drug for treating it. Only by abandoning organ-specific and embracing multidisciplinary holistic and individualized approach to treatment of our patients we can count on improvements in all outcomes.

Perhaps we should not be too modern and should go back to what Sir William Osler, often referred to as The Father of Modern Medicine, has once taught us.

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