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EDITORIAL

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A call to action for fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide, affects nearly 30% of adults in the general population[1] and approximately 70% of those with obesity and type 2 diabetes (T2DM)[2] and is already among the top indications for liver transplantation in most high-income countries. In the last decade, it has become evident that NAFLD is a multisystemic disease,[3] which is associated not only with adverse hepatic outcomes but also with relevant extra-hepatic complications, such as T2DM,[4] cardiovascular disease (CVD),[5] chronic kidney disease (CKD)[6] and specific extra-hepatic cancers.[7]

In 2020, a panel of international experts has proposed the change of the terminology from NAFLD to metabolic associated fatty liver disease (MAFLD), as well as an update in the definition of fatty liver disease.[8] Specifically, the diagnosis of MAFLD can be supported by the presence of hepatic steatosis, as detected by serum biomarker scores, imaging methods or histology, in individuals with overweight/obesity, T2DM or multiple metabolic alterations. Given these premises, fatty liver disease is gaining more and more attention in both clinical and basic research. In the last months, *high-quality* data have been published on *Liver International* on this topic, providing some answers and raising new research questions. The results of these studies may have also important public health implications.

1 | NAFLD VERSUS MAFLD: WHERE ARE WE?

From the publication of the proposed novel MAFLD criteria,[8] some observational studies have compared MAFLD and NAFLD criteria for the detection of the hepatic and extra-hepatic complications of fatty liver, providing initial but yet not definitive answers, as recently reviewed.[9,10] Indeed, some but not all studies showed that MAFLD were better than NAFLD criteria at discriminating the risk of especially liver-related complications. In this regard, in a recent study involving 1710 US participants (mean age 46 years; 51% were women; mean body mass index 28 kg/m^2) from the 2017-2018 NHANES cohort, Ciardullo and Perseghin reported that for NAFLD and MAFLD, the weighted prevalence was 37% and 39%, respectively, and risk of advanced liver fibrosis estimated by elastography was 7.5% and 7.4%, respectively. These findings are partly different from those provided by Lin et al,[11] who have used data from the 1988-1994 NHANES, and by other authors.[12,13] In this context, we want to underline three specific points. First, observational studies available so far[11-13] largely differ for participants characteristics, study design and setting. Consequently, they are difficult to compare, and notably, the MAFLD criteria may work differently, depending on the prevalence of different features of dysmetabolism and at-risk alcohol intake. Second, the detection of steatosis was performed by different methods, including ultrasonography, magnetic resonance imaging and liver biopsy. Third, non-invasive markers of liver fibrosis, such as FIB-4 and NAFLD fibrosis score, have limited accuracy, and have yet not been validated in patients with MAFLD. In this regard, in an observational study involving nearly 420 consecutive Asian patients with biopsy-proven MAFLD, Wu et al reported that the FIB-4 cut-off of 1.3 had only 58% sensitivity and 74% specificity for advanced fibrosis.[14] Furthermore, given that the NAFLD fibrosis score considers the presence of diabetes, it tends to overestimate fibrosis risk in patients with this condition.

2 | TWO IS WORSE THAN ONE

Another open question is to understand whether in patients with fatty liver, the risk of hepatic and extra-hepatic complications is further increased by the coexistence of different risk factors, such as at-risk alcohol intake and features of dysmetabolism. In the last decade, observational studies have demonstrated that the simultaneous presence of metabolic syndrome and excessive alcohol consumption is independently associated with mortality. For instance, in a cohort of nearly 4300 individuals with fatty liver followed for 20 years, Younossi et al reported that metabolic syndrome and excessive alcohol consumption were associated with mortality and that the effect of excessive alcohol use was specifically detected in individuals with dysmetabolism.[15] By contrast, in the NHANES cohort including 8162 participants (56% with NAFLD), Hajifathalian et al showed that, among individuals with NAFLD, modest alcohol consumption (0.5-1.5 drinks/day) was associated with a decrease in all-cause mortality whereas high alcohol consumption ($i \geq 1.5$ drinks/day) with increased mortality, over a mean follow-up of 12 years.[16] Scarce information is however available on the impact of dysmetabolism on liver fibrosis in patients with fatty liver stratified by alcohol consumption.

In a population-based study enrolling 1760 Spanish individuals (263 were former drinkers, and 1497 were current drinkers at the time of the study), Pose et al now report that metabolic syndrome was associated with a nearly four-fold higher risk of liver fibrosis (stiffness ≥8 kPa) in individuals with alcohol consumption, pointing

out the additive adverse effect of the metabolic and toxic component of liver fibrosis.[17] These findings support the notion that a stringent control of metabolic risk factors is mandatory for the management of individuals with alcohol-related liver disease. In addition, given that there is now convincing evidence demonstrating that the 'safe' levels of alcohol consumption are near zero,[18] physicians should encourage all patients with fatty liver to abstain from alcohol (impractical though it may seem).

3 | SARCOPENIA AND NAFLD: THERE IS MORE

Another emerging predictor of poor prognosis in individuals with NAFLD is sarcopenia. Some cross-sectional studies and a meta-analysis[19] have documented that sarcopenia is associated with NAFLD, even after adjustment for metabolic confounders. However, information regarding the direct impact of sarcopenia on morbidity and mortality in patients with NAFLD is still scarce. By analysing 11 065 US individuals from the NHANES III (34% with NAFLD on ultrasonography), Kim et al now showed that, during a median follow-up of 23 years, sarcopenia (as diagnosed by bioelectrical impedance) was associated with all-cause mortality in individuals with NAFLD (HR 1.44, 95% CI 1.16-1.80) but not in those without liver involvement.[20] In addition, individuals with both sarcopenia and NAFLD had a higher risk for all-cause mortality (HR 1.28, 95% CI 1.06-1.55), when compared to those without sarcopenia and NAFLD.[20] Interestingly, sarcopenia was significantly associated with a higher risk for cancer- (HR 1.49, 95% CI 1.01-2.20) and diabetes- (HR 4.94, 95% CI 1.70-14.38) related mortality in patients with NAFLD only.[20] These findings support the notion that, in NAFLD patients with sarcopenia, physical activity and dietary interventions aimed to increase skeletal muscle mass may improve clinical outcomes.[21]

4 | NAFLD AND CVD: WHAT'S NEW?

The association between NAFLD and CVD has extensively been studied in the last two decades,[22] clearly documenting that the most common cause of death among patients with NAFLD is cardiovascular events.[23] The magnitude of increase in cardiovascular risk seems to be proportional to the severity of NAFLD.[24] In a recent nationwide, age- and sex-matched cohort study enrolling 10 568 Swedish individuals in with biopsy-confirmed NAFLD (11% with T2DM at baseline) and 49 925 controls (3% with T2DM), Simon et al reported that mortality rates from CVD progressively increased from simple steatosis (HR 1.25, 95% CI 1.16-1.35) to NASH (HR 1.66, 95% CI 1.38-2.01), noncirrhotic fibrosis (HR 1.40, 95% CI 1.17-1.69) and cirrhosis (HR 2.11, 95% CI 1.63-2.73), over a median follow-up of 14 years.[24]

Two novel studies have now been published. In a longitudinal study of 3718 consecutive patients with previous myocardial infarction, Cao et al reported that, compared to those with low values of non-invasive markers of liver fibrosis, those with high values had a higher risk of incident fatal and nonfatal cardiovascular events, over a mean follow-up of 4 years.[25] Importantly, the incorporation of non-invasive markers of liver fibrosis in a prediction model including classical CVD risk factors improved the prediction for incident cardiovascular events.[25] These data suggest that liver fibrosis may be considered as a novel independent predictor for fatal and nonfatal cardiovascular events.

Unfortunately, cardiovascular risk management is still suboptimal in daily clinical practice for NAFLD patients. Using a national digestive disease specialists survey on cardiovascular risk management in Spanish hospitals, Iruzubieta et al documented that, although ~80% clinicians were aware that NAFLD is a strong predictor of cardiovascular events, approximately only one-fifth of respondents performed an elementary physical examination to address the cardiovascular risk, nearly 50% spent less than 5 min providing lifestyle advice and approximately 52% did not start any drug treatment after a recent diagnosis of any CVD.[26] Given the strong evidence in support,[3,5,23,27] this attitude may be no longer justifiable. In this regard, it is important to remember that, in a post hoc analysis of GREACE randomized controlled study enrolling 437 patients with moderately abnormal liver tests at baseline due NAFLD, Athyros et al documented that NAFLD patients who received atorvastatin had significantly reduced cardiovascular morbidity and a decrease in alanine aminotransferase (ALT) levels without significant liver-related adverse events.[28]

Statin treatment was also associated with less severe steatosis, inflammation and fibrosis in patients with NAFLD,[29,30] although carriage of the I148 M *PNPLA3* risk variant, the main genetic determinant of progressive liver disease[31] may limit beneficial effects.[29] In a recent observational study of 11 593 409 individuals from the National Health Information Database of the Republic of Korea (712 262 of whom had NAFLD), Lee et al showed that the statin use was independently associated with a reduced risk of NAFLD (OR 0.66, 95% CI 0.65-0.67), as well as with a reduced risk of significant liver fibrosis (OR 0.43, 95% CI 0.42-0.44).[30] Similar considerations might be done for specific antihypertensive agents, such as renin-angiotensin axis modulators.[32,33] At present, there are still few data on the effects of various antiplatelet agents on liver fibrosis in patients with NAFLD.[34]

Large randomized controlled trials focused on treatments for liver disease with systematic evaluation of cardiovascular outcomes are still needed to establish a causal association between fatty liver disease and CVD. For now, there is already ample evidence supporting the early and aggressive treatment of the coexisting cardiometabolic comorbidities in all patients with NAFLD.

5 | KEY MESSAGES

The current evidence supports the notion that NAFLD is a multisystem disease,[3] with dramatic consequences not only from the clinical point of view but also from the economic point of

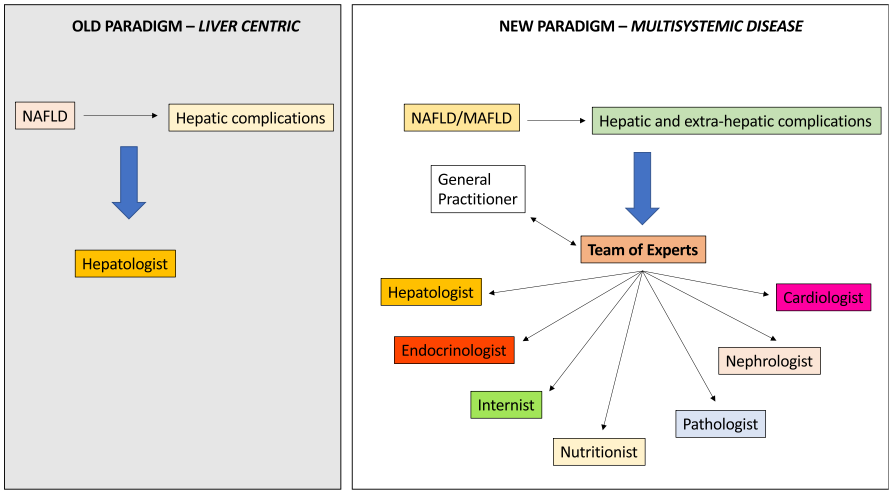

FIGURE 1 The old paradigm that NAFLD is only associated with hepatic complications is no longer valid. A large body of evidence now indicates that NAFLD/MAFLD is also associated with serious extra-hepatic complications, thereby requiring a team of experts for a multidisciplinary management approach

view.[35] In this regard, recently, Schattenberg et al clearly documented a dramatic economic impact of nonalcoholic steatohepatitis (NASH) in adults living in five European countries, namely, France, Germany, Italy, Spain and the United Kingdom.[35] Hence, earlier diagnosis and care of NAFLD and its consequences may contribute to reduce future healthcare impact and costs. In doing this, a 'liver-centric' approach to NAFLD is no longer sufficient. Unfortunately, the awareness of this is not yet deep-rooted among clinicians.[26] An individualized and holistic management of NAFLD/MAFLD patients with relevant metabolic comorbidities (such as T2DM, obesity, dyslipidemia, hypertension and CVD) by a team of experts, including not only hepatologists but, starting from general practitioners, involve also endocrinologists, internists, cardiologists and pathologists, will be key and increasingly necessary (Figure 1). Such effort might provide the basis for a more rational approach to manage fatty liver disease and its consequences, thereby attenuating its global burden and economic impact.

KEYWORDS

fatty liver disease; metabolic-associated fatty liver disease, hepatic steatosis, liver fat, MAFLD; nonalcoholic fatty liver disease, NAFLD; nonalcoholic steatohepatitis, NASH

CONFLICT OF INTEREST

The authors have nothing to declare.

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