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Commentary

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MASLD co-aggregates with HCC in families-names change, fa(c)ts remain

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Abstract

My invited commentary discusses a recent paper published by Ebrahimi *et al.*[28]. To this end, the definitions of nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), and the most recently proposed metabolic dysfunction-associated steatotic liver disease (MASLD) are reviewed. For brevity, the overarching definition of metabolic fatty liver syndromes (MFLS) is utilized to allude to NAFLD/MAFLD/MASLD collectively, although each nomenclature identifies different diagnostic criteria and distinct patient populations. Ebrahimi and colleagues conducted an analysis using data from the National Swedish Multigeneration archive, involving 38,018 MASLD first-degree relatives (FDRs) and 9,381 MASLD spouses, alongside 197,303 comparator FDRs and 47,572 comparator spouses. These authors followed these groups for a median of 17.6 years and reported a definite familial aggregation of adverse liver-related events among families of MASLD individuals. These events comprise increased relative risks of hepatocellular carcinoma (HCC), major chronic liver disease, and mortality owing to hepatic causes. I comment on this study with reference to the ongoing changes in terminology describing MFLS and to sexual dimorphism exhibited by MFLS. It is concluded that the study by Ebrahimi adds another piece to the puzzle of knowledge requested to implement those precision medicine approaches that are eagerly awaited in the field of MFLS.

Keywords: HCC, MAFLD, MASLD, MFLS, NAFLD, NASH, precision medicine

CONTEXT

It is widely appreciated that, compared to primitive human populations, modified lifestyle habits expose contemporary men to the risks inherent in sedentary behavior, overnutrition, obesity, and challenges of other exogenous offending agents, which may eventually harm liver health in the setting of subclinical chronic inflammation and lipotoxicity[1]. The liver exerts various vital activities spanning from digestive, metabolic, immunological, and purificatory physiological functions but has limited capacities to deal with the enormous increase of calories provided by food, soft drinks, and alcoholic beverages and with other noxious agents[2]. The ensuing health risks may particularly occur within families, given that parental obesity alters metabolic programs in the progeny, predisposing them to adult-onset metabolic syndrome[3].

DEFINITIONS-NAFLD/MAFLD/MASLD

First coined in the 1980s, the acronym NAFLD eventually came to embrace a histological spectrum including the more stable steatosis, the more rapidly progressive nonalcoholic steatohepatitis (NASH), (cryptogenic) cirrhosis, and hepatocellular carcinoma (HCC) arising in the context of steatosis and/or NASH[4-7]. The "negative" qualification inherent in the NAFLD definition was deemed essential, at that time, to highlight the striking similarity of the above-depicted spectrum with alcohol-related liver disease, which was, however, observed in the nonalcoholic[8]. Indeed, rather than being exposed to an exogenous trigger (i.e., hepatotoxic amounts of alcohol), NAFLD individuals often exhibit metabolic dysfunction when first observed and are also prone to manifesting incident features of the metabolic syndrome during a 5-year follow-up[9,10]. Based on solid histological grounds, the NAFLD nomenclature requests excluding, further to alcohol, also other competing etiologies of chronic (steatogenic) liver disease (CLD), namely viral infection, drug-induced conditions, autoimmune disorders, genetic factors, and dysthyroidism; however, the extent to which these competing etiologies should be ruled out remains incompletely defined[11].

The abundant literature associating NAFLD with the risk of incident HCC[12] has eventually resulted in the recommendation, in clinical practice, to optimize the implementation and effectiveness of surveillance protocols among at-risk patients with NAFLD[13]. However, the cost/effectiveness ratio of HCC surveillance in NAFLD needs further evaluation and surveillance using ultrasound alone may guarantee insufficient diagnostic accuracy, particularly in the setting of obesity[13].

In 2020, various authors agreed on the notion that "nonalcoholic" should best be replaced with a "positive" diagnostic criterion, i.e., metabolic dysfunction-associated fatty liver disease (MAFLD)[14,15]. MAFLD is defined based on hepatic steatosis (which can be identified non-invasively) associated with one out of three requirements: expanded adipose tissue (defined as either overweight or obesity), type 2 diabetes (T2D), or dysregulated metabolism (namely ≥ two among enlarged waist circumference; arterial hypertension; and atherogenic dyslipidemia)[12]. MAFLD criteria include individuals with other chronic liver diseases who, conversely, are excluded from the NAFLD definition. This makes MAFLD a very inhomogeneous descriptor, given that it comprises individuals with liver disease owing to different (and sometimes multiple) etiologies such as alcohol, viral hepatitis, and others, which may potentially carry a variable risk of developing liver-related outcomes, including HCC. However, there is no clear-cut evidence that MAFLD captures HCC risk better than MAFLD, while, as expected, those with concurrent NAFLD and MAFLD are at increased risk of HCC[16].

In 2023, concerns that "fatty" could invariably be stigmatizing for disease stakeholders, which remains unproven[17], has led a multi-society Delphi consensus statement to renaming MAFLD to MASLD, where "fatty" has been converted into its synonym "steatotic"[18]. A large panel of International Experts agreed in highlighting the close link between MASLD and cardiometabolic risk to include, in the MASLD definition,

the presence of ≥ 1 out of 5 cardiometabolic risk factors, in addition to hepatic steatosis[18].

Interestingly, "steatotic" was intended to be a less stigmatizing term than fatty, although the prefix "steato" means nothing else but "fatty"[19]. Of concern, "steatotic" is not identifiable in common sources[20-23]. This implies that patients receiving the MASLD diagnosis will remain totally dependent on medical explanations regarding their health status. Of concern, allegations that "fatty" is a stigmatizing qualification globally remain unproven[24], weakening the rationale of this change of nomenclature.

In this evolving context, recent studies tend to use MASLD as a synonym for NAFLD, although additional prospective studies conducted by independent investigators will provide convincing evidence that the two nosographies are indeed fully equivalent, as suggested by recent investigations[25].

To overcome the potentially relevant differences across the NAFLD-to-MAFLD-to-MASLD transition, I will use the expression "metabolic fatty liver syndromes" (MFLS) in my editorial to indicate the whole spectrum of hepatic conditions discussed above: NAFLD/MAFLD/MASLD. This is not to deny that each name identifies distinct patient populations, but only for conciseness' sake.

The MFLS nomenclature offers, in my opinion, the advantage of utilizing the requested positive criterion "metabolic", while also highlighting (therefore "syndrome") the acknowledged disease heterogeneity owing to multiple pathogenic drivers, and different factors and cofactors, that interact in the individual patient to a variable extent accounting for variable disease outcomes[25-27].

THE PAPER BY EBRAHIMI AND COLLEAGUES

Ebrahimi *et al.* leveraged the Swedish Multigeneration archive to recruit 38,018 MASLD first-degree relatives (FDRs) defined as: parents, siblings, offspring, and 9,381 spouses to MASLD patients; 197,303 comparator FDRs and 47,572 comparator spouses[28]. The study included a median 17.6-year follow-up.

Cox proportional hazards models were used to compute adjusted Hazard Ratios (aHRs) for HCC, major hepatic events (namely cirrhosis, decompensated CLD, or liver transplantation), mortality owing to CLD, non-hepatic cancer, and mortality owing to causes other than CLD.

With specific reference to the odds of HCC, authors have found that, at the end of follow-up, the risk of incident HCC was more elevated among MASLD FDRs than in comparator FDRs (13 *vs.* 8/100,000PY; aHR = 1.80, 95%CI = 1.36-2.37), being particularly high among FDRs related to probands who had either hepatic fibrosis or liver cirrhosis (aHR = 2.14, 95%CI = 1.07-4.27; *P* Heterogeneity = 0.03).

Additionally, secondary findings of the study were that FDRs of MASLD patients exhibited increased odds of major hepatic events (73 *vs.* 20 51/100,000PY; aHR = 1.52, 95%CI = 1.36-1.69) and mortality owing to hepatic causes (20 *vs.* 21 11/100,000PY; aHR = 2.14, 95%CI = 1.67-2.74).

Authors conclude that, although there is a definite familial aggregation of liver-related events among families of patients with biopsy-proven MASLD, including increased relative risks of HCC, major CLD, and mortality owing to hepatic causes, risks are low in absolute terms.

COMMENT

This study elegantly illustrates the important notion that the entire spectrum of MFLS results from the

Table 1. Insulin resistance, NAFLD, advanced hepatic fibrosis, and HCC cluster among families

Author[Ref], year	Series	Finding	Comment
Abdelmalek *et al.*[30], 2006	20 NAFLD patients and 20 age-, sex-, and BMI-matched controls with ≥ 4 living relatives and 2 generations of lineage	IR and diabetes occurred more often among NAFLD patients' rather than among controls' first-degree relatives (P = 0.042, and P = 0.013; OR, 2.86; 95%CI, 1.02-9.38; P = 0.042; and OR, 4.2; 95%CI 1.26-18.7; P = 0.013, respectively)	Familial clustering of IR and diabetes support a genetic predisposition for NAFLD
Hassan *et al.*[31], 2009	347 HCC patients and 1,075 healthy controls	HCC in first-degree relatives was a risk factor for HCC development irrespective of infections with either HBV or HCV. [AOR = 4.1 (95%CI, 1.3-12.9)]	First-degree family history of HCC is a risk factor for HCC development in the USA
Caussy *et al.*[32], 2017	26 NAFLD-cirrhosis patients, and 39 FDRs were compared to 69 community-dwelling twins, sib-sib, or parent-offspring pairs (n = 138), comprising 69 NAFLD-free individuals and 69 of their FDRs	The risk of advanced liver fibrosis remained significantly associated with the condition of being FDRs of patients with NAFLD-cirrhosis (aOR 12.5; 95%CI, 1.1-146.1, P = 0.0438) irrespective of the following confounding factors: age, sex, ethnicity, BMI, and diabetes	FDRs of NAFLD-cirrhosis patients exhibit a 12-fold increased risk of having advanced fibrosis, which supports the consideration of screening these individuals for hepatic fibrosis
Tamaki *et al.*[33], 2022	396 FDRs (220 in a derivation cohort and 176 in a validation cohort)	The independent predictors of advanced fibrosis at multivariable-adjusted LRA were age ≥ 50 years; male sex; having a FDR with NAFLD with advanced fibrosis; and diabetes (aORs: 2.63, 95%CI 1.0-6.7; 3.79, 95%CI 1.6-9.2; 3.37, 95%CI 1.3-9; 11.8, 95%CI 2.5-57, respectively, all P < 0.05)	Being FDRs of probands with NAFLD with advanced fibrosis carries a significantly increased risk of having advanced hepatic fibrosis
Anand *et al.*[34], 2022	447 family members of 191 NAFLD patients	The prevalence of NAFLD among seemingly healthy NAFLD individuals was 55.9% *vs.* a prevalence of NAFLD in the same geographical area reportedly spanning from 16% to 32%	In India, family members of patients with NAFLD are at increased risk of NAFLD compared to the general population

aOR: adjusted Odds Ratio; BM: body mass index; CI: confidence intervals; FDRs: first-degree relatives; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; IR: insulin resistance; LRA: logistic regression analysis; NAFLD: nonalcoholic fatty liver disease; USA: United States of America.

synergy of genetic predisposition and lifestyle-related modifiers[25]. However, it is difficult to split the former predisposition from the latter modifiers owing to the failure of Ebrahim and colleagues to analyze the genetic background of spouses and, therefore, to segregate the effects of genetics from those of lifestyle habits, notably including diet and physical activity/exercise, and of exposure to environmental carcinogens. In this regard, important advances in our understanding of genetic polymorphisms involved in the development and progression of MFLS[29] seemingly retard entering the clinical arena.

Moreover, the research by Ebrahimi *et al.* has important clinical implications[28]. Recently, it has been recommended that FDRs of individuals with MASLD-cirrhosis should invariably be offered an assessment aimed at identifying progressive hepatic fibrosis[18]. It is worth noting that, based on data published by Ebrahimi *et al.*, the above recommendation should be extended also to those FDR of patients with MASLD-fibrosis, therefore widening the scope of family screenings in the field of MFLS[28].

Previous studies, summarized in the Table 1[30-34], have well documented the odds of insulin resistance, NAFLD, advanced liver fibrosis, and HCC cluster among families.

As illustrated by these authors[28], their research exhibits multiple points of methodological strength. For example, the nationwide Swedish Multigeneration archive enabled the identification of distinct sub-cohorts displaying variable proportions of genetic and environmental cofactors, minimizing the perils of bias. Additionally, this Registry enabled the conduct of follow-up to an extent not otherwise achievable in epidemiological contexts.

Regarding the potential limitations, the authors utilized a nationwide biopsy registry that goes back to years when the MASLD diagnosis had not been proposed yet. Therefore, these patients had NAFLD[35], not MASLD, and it is unclear how metabolic dysfunction (not requested by NAFLD definition) was retrospectively identified in the authors' large-scale cohort. However, a recent study has confirmed that NAFLD and MASL overlap to a substantial extent and, therefore, have the same natural history[36].

Furthermore, although authors tested their findings across various sensitivity analyses, it is important to remember that the development and/or progression of metabolic disorders, MFLS, and HCC all exhibit a strong sexual dimorphism[37-43]. This feature justifies processing data separately by sex, such as specifically recommended in the NAFLD field, to fill our knowledge gap in this arena[44].

Moreover, it must also be highlighted that the proportion of HCC events was limited, particularly so among those who were free of chronic viral hepatitis and alcohol abuse. Finally, it is worth pinpointing the paucity of granular data on ethnicity, alcohol consumption, smoking status, anthropometric indexes (e.g., BMI and waist circumference), some laboratory parameters, and liver elastography.

In conclusion, the study by Ebrahimi[28] adds another important piece to the complex puzzle of knowledge necessary for the successful implementation of precision medicine approaches eagerly anticipated in MFLS research and practice[45-50]. However, the above drawback of the study calls for additional investigations specifically addressing these limitations.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

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Ethical approval and consent to participate

Not applicable.

Consent for publication

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