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INVITED COMMENTARY

Liver, Heart, Death… Can This Sequence Be Broken?

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Non-alcoholic fatty liver disease (NAFLD) is a condition characterized by the accumulation of fat in the liver associated with a range of metabolic disorders, such as obesity, insulin resistance, and dyslipidemia. NAFLD, which has become increasingly prevalent worldwide, affects up to 25% of the general population and is considered a major public health issue [1, 2]. The disease ranges from simple hepatic steatosis to liver cirrhosis. Liver fibrosis is the most important prognostic factor in NASH; the severity of fibrosis as assessed by liver biopsy is strongly associated with the risk of disease progression to cirrhosis- and liver-related mortality [3]. Nevertheless, overall mortality is significantly influenced by other contributing factors, such as malignancy or co-existent cardiac conditions. In fact, patients with NAFLD are particularly at risk for cardiovascular disease (CVD), which is the leading cause of mortality in this population. Individuals with NAFLD have a two to four times increased risk of CVD compared to those without the condition [4]. Though the underlying mechanisms that link NAFLD to CVD are not fully understood, they may involve the release of pro-inflammatory cytokines from the liver, oxidative stress, and changes in lipid metabolism. Insulin resistance, a hallmark of NAFLD, may contribute to the development of CVD by promoting atherosclerosis and endothelial dysfunction [5].

Metabolic risk factors contribute to the development and progression of NAFLD and are often present in patients with the disease. Therefore, an aim of the new definition of metabolic-associated fatty liver disease (MAFLD) was to provide a more accurate and comprehensive approach to diagnosing and managing this complex condition. NAFLD is usually characterized by the accumulation of excess fat in the liver of individuals who consume little to no alcohol. The spectrum of NAFLD ranges from simple fatty liver to the more severe form non-alcoholic steatohepatitis (NASH), which involves liver inflammation and can progress to liver fibrosis, cirrhosis, and even liver cancer. MAFLD describes a range of conditions involving fatty liver disease and metabolic dysfunction. NAFLD is typically diagnosed based on evidence of fatty liver on imaging or histology, along with the exclusion of other liver diseases and significant alcohol consumption. In contrast, MAFLD uses a broader set of diagnostic criteria, including evidence of hepatic steatosis (fatty liver) and the presence of one of three criteria: overweight/obesity, type 2 diabetes, or evidence of metabolic dysregulation (e.g., insulin resistance, dyslipidemia).

The new definition was developed to address the limitations of the previous definition, which relied solely on the exclusion of other liver diseases and did not sufficiently account for the metabolic dysfunction that underlie the development and progression of MAFLD.

The current guidelines of the professional societies do not recommend a routine assessment of the cardiovascular status in NAFLD patients, which appears to be appropriate since this is marked patient heterogeneity terms of mortality risk. This population ranges from the young, slightly overweight patient with mild steatosis to older patients with more severe fibrosis- and insulin-dependent diabetes.

In this issue of *Digestive Diseases and Sciences*, McNally and colleagues [6] address the question of which patients with fatty liver disease have an increased cardiovascular risk, with the intent of identifying a specific at-risk subpopulation. In this single-center retrospective study, they examined the risk of CVD in 5288 patients with hepatic steatosis classified as NAFLD-MAFLD, non-MAFLD NAFLD, and non-NAFLD MAFLD, depending on whether they met the definition of one or both conditions. They also examined the possible association between advanced liver fibrosis (defined by FIB-4) and CVD in different subgroups. With this approach, the authors ensured that both the influence of metabolic factors (distinguishing between MAFLD/NAFLD) and that of advanced liver disease (fibrosis) are determined.

Of the 5288 patients enrolled, 13.5% had concomitant CVD. A total of 2821 patients with steatosis and metabolic

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risk without concomitant liver disease were classified as NAFLD-MAFLD of whom 18% had CVD. A total of 1,245 patients with steatosis and no metabolic risk and no concomitant liver disease were classified as non-MAFLD-NAFLD of whom 2.2% had CVD. 812 patients had metabolic risk and other potential contributors to liver disease and were classified as non-NAFLD-MAFLD of whom 19.2% had CVD. Using multivariate analysis, Fib-4 < 2.67 was determined to be an independent risk factor for CVD in the overall fatty liver disease cohort and in the NAFLD-MAFLD subgroup. Fib-4 as a continuous variable had a linear association with CVD risk in the overall, fatty liver disease, non-MAFLD NAFLD, and NAFLD-MAFLD groups starting at Fib-4 levels < 2.67. Nonetheless, the overall median Fib-4 was lowest in the non-MAFLD NAFLD group, suggesting that metabolic conditions promote progression of liver disease.

Since the combination of several metabolic risk factors such as diabetes, arterial hypertension, and progressives NASH increase the risk of developing hepatocellular carcinoma (HCC) [7, 8], the European Association for the Study of the Liver (EASL) has expanded its recommendations for HCC screening. Regarding cardiovascular risk factors, patients meeting the criteria for MAFLD are at higher cardiovascular risk [9]. The McNally study confirmed that only the MAFLD cohort ultimately had a significantly increased risk of CVD. Furthermore, a Korean population study showed that MAFLD may better identify individuals at risk for CVD than NAFLD, ultimately supporting the role of metabolic comorbidities [10].

The current work certainly has some limitations. First, data collection was based on ICD codes that are user dependent adding considerable variability regarding which diagnostic tool was used to diagnose fatty liver. Furthermore, only a non-invasive fibrosis score was used to assess fibrosis. Also, with regard to the outcome, the severity of CVD and which diagnostic tool led to the diagnosis was not clarified. Furthermore, due to the methodology, the authors were not able to collect anthropomorphic data, such as BMI, abdominal circumference, and HOMA-IR, which are ultimately part of the MAFLD definition and therefore represent a bias.

Though, it may be tempting for some to postulate that simple steatosis without metabolic risk factors is therefore not dangerous, caution is needed. It would be more apt to interpret the data as a journey through time: the NAFLD-non-MAFLD cohort was simply younger. As such, the data collected here are another indication that NAFLD and MAFLD are not independent entities, but rather fatty liver disease is the beginning of an accumulation and progression of multiple metabolic disorders that all too often end with a cardiovascular event.

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Declarations

Conflict of interest Nothing to report.

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