Advances in Research on the Association Between Non-alcoholic Fatty Liver Disease, Metabolic-Associated Fatty Liver Disease, and Cardiovascular Disease: A Postprint

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease worldwide. In recent years, numerous studies have demonstrated its close association with metabolic dysfunction, leading expert panels to propose renaming it metabolic dysfunction-associated fatty liver disease (MAFLD). NAFLD/MAFLD not only may lead to increased incidence and mortality of liver-related diseases, but is also associated with the onset and mortality from cardiovascular disease. This article compares the diagnostic criteria for NAFLD/MAFLD and summarizes research progress on the association between NAFLD/MAFLD and cardiovascular disease. The results demonstrate that both NAFLD/MAFLD exhibit significant correlations with increased incidence of cardiovascular disease, are independent influencing factors for cardiovascular disease, and that MAFLD patients have a higher risk of developing cardiovascular disease than NAFLD patients. This article provides clinicians with a basis for cardiovascular risk assessment and management in NAFLD/MAFLD patients, suggesting that when managing NAFLD/MAFLD patients, clinicians should, in addition to focusing on treatment of liver disease, also pay attention to the risk of developing cardiovascular disease.

Full Text

Research Progress in the Correlation of Non-alcoholic Fatty Liver Disease and Metabolic-associated Fatty Liver Disease with Cardiovascular Diseases in China and Abroad

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease worldwide. Numerous recent studies have demonstrated its close correlation with metabolic disorders, prompting an expert panel to propose renaming it metabolic-associated fatty liver disease (MAFLD). NAFLD/MAFLD may not only increase the incidence and mortality of liver-related diseases but also correlate with the incidence and mortality of cardiovascular diseases. This article compares the diagnostic criteria for NAFLD/MAFLD and reviews research progress on their association with cardiovascular diseases. The results show that both NAFLD and MAFLD are significantly associated with increased cardiovascular disease incidence and represent independent risk factors for cardiovascular disease, with MAFLD patients facing higher cardiovascular risk than NAFLD patients. This article provides clinicians with a basis for cardiovascular risk assessment and management in NAFLD/MAFLD patients, emphasizing that clinicians should focus on cardiovascular disease risk in addition to liver disease treatment when managing NAFLD/MAFLD patients.

Keywords: Non-alcoholic fatty liver disease; Metabolic associated fatty liver disease; Cardiovascular diseases; Association study

Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to a hepatic metabolic disorder characterized by excessive fat deposition in hepatocytes, excluding cases caused by long-term heavy alcohol consumption and other defined liver injuries. It is the most common chronic liver disease globally, with a prevalence of approximately 25% among adults worldwide [1-2]. Evidence indicates that NAFLD is closely linked to metabolic dysfunction. In March 2020, an international expert panel proposed replacing NAFLD with the new term "metabolic-associated fatty liver disease (MAFLD)." While many domestic and international hepatology experts support this renaming, controversy remains [3-4]. NAFLD and MAFLD differ in both definition and diagnostic criteria. Recent studies have shown that both conditions are closely associated with cardiovascular disease and may represent independent risk factors for cardiovascular disease [5-8]. This article compares the diagnostic criteria for NAFLD and MAFLD and reviews studies on their association with cardiovascular disease incidence and mortality.

1. Literature Search Strategy

We conducted computerized searches of PubMed, CNKI, Wanfang Data, VIP, and other databases from inception to August 2022. Chinese search terms included "non-alcoholic fatty liver disease," "metabolic-associated fatty liver disease," "cardiovascular disease," and "diagnostic criteria." English search terms included "non-alcoholic fatty liver disease," "metabolic-associated fatty liver disease," "cardiovascular disease," and "diagnostic criteria." Inclusion criteria comprised literature addressing the impact of NAFLD on cardiovascular disease, the impact of MAFLD on cardiovascular disease, the renaming of NAFLD, and MAFLD diagnosis. Exclusion criteria included articles unrelated to the topic, poor-quality studies, or inaccessible articles. Relevant articles were ultimately included for analysis.

2. Diagnostic Criteria

2.1 NAFLD Diagnosis Based on the degree of hepatic steatosis, NAFLD can be classified into non-alcoholic simple fatty liver (NAFL), non-alcoholic steatohepatitis (NASH) and its associated cirrhosis and hepatocellular carcinoma (HCC). NASH may progress to hepatic fibrosis. Currently, NAFLD diagnosis requires imaging or histological evidence of excessive fat deposition (steatosis) in hepatocytes, with no history of heavy alcohol consumption, no competing etiologies for steatosis, and no coexisting causes of chronic liver disease. After excluding other causes of hepatic steatosis, NAFLD can be diagnosed [9-11].

2.2 MAFLD Diagnosis According to the international expert consensus published in March 2020, MAFLD is diagnosed when imaging, hepatic blood biomarkers, or biopsy histology indicate fatty liver disease combined with one of three conditions: overweight/obesity, type 2 diabetes, or the presence of two or more metabolic risk abnormalities [3]. Patients with hepatic steatosis and a BMI $\geq$ 23.0 kg/m^2 (for Asian populations) or diagnosed with type 2 diabetes can be directly diagnosed with MAFLD. Additionally, in patients with type 2 diabetes or obesity, MAFLD is diagnosed when metabolic risk abnormalities are present, including at least two abnormal indicators among seven criteria: waist circumference, blood pressure, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose, insulin resistance index, and high-sensitivity C-reactive protein.

3. Association Between NAFLD/MAFLD and Cardiovascular Disease

3.1 NAFLD and Cardiovascular Disease Studies have shown that NAFLD is an independent risk factor for cardiovascular disease, with NAFLD patients facing higher cardiovascular risk [12]. NAFLD increases cardiovascular disease incidence and mortality, with risk escalating as disease severity increases [13].

3.1.1 NAFLD and Cardiovascular Disease Incidence and Mortality (1) Association with cardiovascular incidence: An 8-year cohort study by Henson et al. [14] demonstrated that advanced fibrosis in biopsy-confirmed NAFLD patients was a significant predictor of cardiovascular disease (HR = 2.86, 95% CI: 1.36–6.04). Similarly, a prospective cohort study by Baratta et al. [15] found that NAFLD patients had more than double the cardiovascular disease risk (HR = 2.41, 95% CI: 1.06–5.47), while those with concurrent hepatic fibrosis had over four times the risk (HR = 4.02, 95% CI: 1.21–13.38). A 20-year community-based cohort study showed that NAFLD incidence increased fivefold over two decades, particularly among younger populations, with cardiovascular disease incidence reaching 34% in those with NAFLD versus 22% in controls [16]. A meta-analysis by Targher et al. [17] of 16 cohort studies (9 prospective, 7 retrospective) including 34,043 adults with a median follow-up of 7 years (36.3% with NAFLD) revealed that NAFLD patients had 64% higher risk of fatal or non-fatal cardiovascular events compared to those without NAFLD (OR = 1.64, 95% CI: 1.26–2.13).

(2) Association with cardiovascular mortality: A cohort study by Caruso et al. [18] in southern Italy found no statistically significant correlation between NAFLD presence/severity and cardiovascular or cancer-related mortality. However, Kim et al. [19] using U.S. NHANES III data demonstrated that advanced NAFLD was associated with increased cardiovascular mortality (HR = 2.53, 95% CI: 1.33–4.83). Additionally, a Swedish nationwide cohort study similarly showed NAFLD was associated with cardiovascular mortality (HR = 1.35, 95% CI: 1.26–1.44) [20].

These findings indicate that NAFLD is associated with increased cardiovascular incidence, particularly in severe NAFLD or NASH populations. However, studies on NAFLD and cardiovascular mortality have yielded inconsistent results, possibly due to the small proportion of advanced NAFLD patients in overall cohorts. In summary, advanced NAFLD shows stronger associations with cardiovascular mortality, while mild-to-moderate NAFLD shows weaker mortality associations but stronger incidence associations.

3.1.2 NAFLD and Specific Cardiovascular Diseases (1) Association with arterial hypertension: Arterial hypertension is the most common modifiable cardiovascular risk factor. Studies have demonstrated that 40–70% of NAFLD patients have arterial hypertension, with NAFLD closely associated with hypertension risk [21-22]. A Finnish study found that NAFLD patients with hepatic steatosis on ultrasound had significantly higher 24-hour, daytime, and nighttime mean systolic and diastolic blood pressure compared to non-NAFLD patients, in both hypertensive and normotensive subjects [23].

(2) Association with coronary heart disease: Studies have proven that NAFLD is closely associated with coronary heart disease risk and exacerbates subclinical atherosclerosis and coronary artery disease risk [24]. One study showed that NAFLD populations had 32% higher atherosclerosis risk compared

to controls, with risk increasing as NAFLD severity progressed (HR = 1.59, 95% CI: 1.21–2.08 for moderate-to-severe NAFLD) [25]. In patients without hypertension and diabetes, coronary heart disease was associated with NAFLD, with severe NAFLD even predicting coronary heart disease risk [26].

(3) Association with other cardiac diseases: Beyond coronary heart disease risk, NAFLD may cause diastolic and systolic left ventricular hypertrophy and cardiac remodeling, increasing risks of cardiomyopathy, cardiac valve calcification, and arrhythmias [27-28]. Cohort studies have shown that NAFLD is significantly associated with increased arrhythmia recurrence after atrial fibrillation ablation, suggesting that early identification and reversal of NAFLD could improve survival in arrhythmia patients when possible [29].

3.2 MAFLD and Cardiovascular Disease Current research on MAFLD and cardiovascular disease remains limited, with most studies comparing MAFLD and NAFLD. These studies indicate that MAFLD patients have significantly higher cardiovascular disease incidence and mortality compared to non-MAFLD populations [30].

3.2.1 MAFLD and Cardiovascular Disease Incidence and Mortality
(1) Comparison of MAFLD and NAFLD with cardiovascular incidence: A 4.6-year cohort study of 6,873 subjects in Shanghai by Liang et al. [31] showed that MAFLD baseline prevalence was higher than NAFLD and associated with cardiovascular disease incidence (HR = 1.44, 95% CI: 1.15-1.81). Guerreiro et al. [32] similarly noted that both NAFLD and MAFLD patients with biopsy-confirmed hepatic steatosis had high cardiovascular disease incidence, but MAFLD patients had higher incidence and risk than NAFLD patients. A Korean cohort study found that the HR for cardiovascular disease was 1.09 (95% CI: 1.03–1.15) in NAFLD-only patients, 1.43 (95% CI: 1.41–1.45) in MAFLD-only patients, and 1.56 (95% CI: 1.54–1.58) in patients with both conditions [33]. This suggests that applying MAFLD criteria may identify more individuals with complex metabolic fatty liver disease and increased cardiovascular risk [33]. A Japanese retrospective study showed that both MAFLD and NAFLD patients had increased cardiovascular disease incidence (HR = 2.69, 95% CI: 2.55–2.83 for MAFLD; HR = 2.82, 95% CI: 2.64–3.01 for NAFLD), with higher rates of diabetes and hyperlipidemia complications that may influence cardiovascular disease development [34].

(2) Association with cardiovascular mortality: A prospective community cohort study by Moon et al. [35] with 15.7 years of follow-up found that MAFLD increased all-cause mortality risk after adjusting for multiple factors (HR = 1.36, 95% CI: 1.08–1.73), but showed no statistically significant association with cardiovascular mortality. Similarly, using U.S. NHANES III data, Kim et al. [36] found that MAFLD was associated with all-cause mortality (HR = 1.17, 95% CI: 1.04–1.32) after adjusting for demographics, traditional risk factors, and metabolic factors, but neither NAFLD nor MAFLD showed significant associa-

tions with cardiovascular mortality.

3.2.2 MAFLD and Specific Cardiovascular Diseases (1) Association with hypertension: A baseline study from the Jinchang cohort in China showed that MAFLD patients had hypertension incidence approaching that of NAFLD patients, but the incidence density was 47.29 per 1,000 person-years, higher than in NAFLD patients and 1.70 times that of normal populations. Patients with both MAFLD and NAFLD showed significantly elevated hypertension incidence (HR = 1.791, 95% CI: 1.539–2.083) [37].

(2) Association with other cardiovascular diseases: Studies have shown that MAFLD patients have risks of cardiac systolic and subclinical systolic dysfunction, as well as diastolic dysfunction. MAFLD patients have lower glycine-tyrosine levels than non-MAFLD patients ($P < 0.001$), with reduced glycine-tyrosine levels correlating with left ventricular systolic dysfunction. Compared to non-MAFLD groups, MAFLD patients showed increased E/e' ratio ($P = 0.008$) and cardiac output ($P = 0.034$) [38]. Additional research indicates that MAFLD patients have higher cardiomyopathy risks, such as left ventricular systolic and/or diastolic dysfunction and hypertrophy, which may lead to heart failure, cardiac valve calcification (primarily aortic valve sclerosis), arrhythmias (e.g., atrial fibrillation, ventricular arrhythmias), and certain types of cardiac conduction defects over time [39].

Since the MAFLD definition was proposed in 2020 and gradually gained acceptance, research on its association with specific cardiovascular diseases remains limited. Future studies should further explore these relationships to identify specific factors and mechanisms in cardiovascular disease development among MAFLD patients, enabling personalized treatment approaches to reduce cardiovascular events and improve outcomes. This research will also help elucidate pathophysiological mechanisms and provide new directions for future investigations.

3.3 Pathogenic Mechanisms of NAFLD and MAFLD in Cardiovascular Disease

Multiple clinical and cohort studies have demonstrated close associations between NAFLD, MAFLD, and cardiovascular disease, though underlying mechanisms require further elucidation. Research indicates that glucose metabolism disorders, visceral fat, dyslipidemia, and insulin resistance are closely related to NAFLD development and progression, while also being determinants of cardiovascular disease onset [40-41], potentially explaining NAFLD-related cardiovascular risk. NAFLD pathophysiology involves insulin resistance, which impairs adipose tissue adipokine production (particularly adiponectin). Increased reactive oxygen species formation leads to enhanced free fatty acid oxidation and triglyceride accumulation through de novo lipogenesis, which may affect atherosclerotic plaque formation and progression, thereby increasing cardiovascular risk in NAFLD patients [42]. Additionally, MAFLD is also associated

with insulin resistance, with advanced NASH symptoms exacerbating hepatic and peripheral insulin resistance, inducing atherogenic dyslipidemia and releasing pro-inflammatory, vasoactive, and prothrombotic molecules that may contribute to hypertension, coronary artery disease, and structural/functional cardiac changes [39]. Studies have also shown that NAFLD-related hepatic lipid metabolism promotes atherosclerosis development, with elevated plasma TG, remnant lipoprotein cholesterol, and LDL penetrating arterial walls to accelerate atherosclerotic plaque progression [43]. An animal study demonstrated that hepatocyte-derived extracellular vesicles under NAFLD conditions induce vascular endothelial inflammation and promote atherosclerosis, suggesting that hepatocyte extracellular vesicles play important roles in long-distance communication between the liver and vascular system, indicating potential novel mechanisms linking NAFLD and cardiovascular disease [44].

4.1 Differences Between NAFLD and MAFLD

NAFLD diagnosis requires exclusion of alcohol-related hepatic steatosis and inaccurately defines disease heterogeneity and its drivers. With increasing fatty liver disease incidence and decreasing average age of onset, research on etiology and pathogenesis suggests that NAFLD's definition poorly reflects disease causes and cannot distinguish whether metabolic or other factors cause fatty liver disease, creating challenges for clinical diagnosis and pharmacotherapy [45]. Additionally, NAFLD' s definition involves alcohol quantification issues, requiring specific drinking thresholds that patients cannot accurately recall, with individual alcohol sensitivity variations further complicating diagnosis. Furthermore, current compound therapies for NAFLD show limited efficacy, partly reflecting that NAFLD' s definition lacks consideration of combined metabolic and alcohol effects on liver function. NAFLD' s exclusive diagnostic approach fails to emphasize metabolic factors' influence, whereas MAFLD provides a more precise definition. Unlike NAFLD' s lack of clear etiological distinction, MAFLD transforms exclusive diagnosis into positive diagnostic criteria, emphasizing metabolic dysfunction' s importance and its association with metabolic diseases. MAFLD incorporates overweight and type 2 diabetes into diagnostic criteria and includes insulin resistance and high-sensitivity C-reactive protein alongside traditional indicators (waist circumference, blood pressure, TG, HDL-C, and glucose), further lowering the threshold for metabolic abnormalities. Overall, MAFLD is superior to NAFLD in clinical diagnosis and treatment by considering more metabolic components [46].

4.2 Implications of Renaming NAFLD to MAFLD

Disease nomenclature should accurately summarize disease characteristics and reflect pathophysiological mechanisms through concise terminology [46]. NAFLD requires excluding other liver injury factors, overemphasizing alcohol while ignoring metabolic dysfunction' s importance. MAFLD' s straightforward definition establishes it as a confirmable disease, facilitating diagnosis and

targeted risk reduction for progressive liver disease. The aforementioned studies show that MAFLD patients have higher cardiovascular disease incidence than NAFLD patients, indicating MAFLD' s definition has stronger cardiovascular disease associations. Clinical adoption of MAFLD will better enable targeted prevention, control measures, and treatments for cardiovascular disease patients, slowing cardiovascular disease development and potentially achieving combined prevention and treatment of MAFLD and cardiovascular disease through metabolic factor control.

In summary, both NAFLD and MAFLD show significant associations with increased cardiovascular disease incidence and represent independent risk factors, with MAFLD patients facing higher cardiovascular risk than NAFLD patients. Current cohort studies show inconsistent results regarding NAFLD's association with cardiovascular mortality, while MAFLD correlates with all-cause mortality but not yet with cardiovascular mortality. This suggests that preventing and treating NAFLD and MAFLD will help slow cardiovascular disease development and reduce incidence. Lifestyle modifications can prevent and treat NAFLD and MAFLD and their associated inflammation and fibrosis, while pharmacological interventions targeting specific metabolic factors can be used for MAFLD [9, 11, 47]. As NAFLD's renaming to MAFLD gains acceptance, future research should deeply investigate MAFLD's pathogenesis, epidemiology, and treatment for clinical application, while also conducting association studies between MAFLD and cardiovascular disease, particularly prospective cohort studies on cardiovascular mortality. Additionally, research should examine MAFLD' s relationship with specific cardiovascular diseases (e.g., arterial hypertension, coronary heart disease) to provide new insights for cardiovascular disease prevention and treatment, offering theoretical foundations for combined prevention and treatment of cardiovascular disease and MAFLD to help patients slow cardiovascular disease progression.

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