Review

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Problems and Challenges Associated with Renaming Non-alcoholic Fatty Liver Disease to Metabolic Associated Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has become the world's largest chronic liver disease in the 21st century, affecting 20%–30% of the world's population. As the epidemiology, etiology, and pathogenesis of NAFLD have been studied in-depth, it has been gradually recognized that most patients with NAFLD have one or more combined metabolic abnormalities known as metabolic syndrome. In 2020, the international expert group changed the name of NAFLD to metabolic-associated fatty liver disease (MAFLD) and proposed new diagnostic criteria for MAFLD and MAFLD-related liver cirrhosis, as well as the conceptual framework of other cause-related fatty liver diseases to avoid diagnosis based on the exclusion of other causes and better reflect its pathogenesis. However, there are still many ambiguities in the term, and changing the name does not address the unmet key needs in the field. The change from NAFLD to MAFLD was not just a change of definition. The problems and challenges are summarized as follows: epidemiology, children, rationality of "metabolism," diagnostic criteria, double/multiple causes, drug discovery, clinical trials, and awareness raising. Metabolic-associated fatty liver disease has complex disease characteristics, and there are still some problems that need to be solved.

Keywords: Non-alcoholic fatty liver disease; Challenge; Hepatic; Metabolic-associated fatty liver disease; Rename

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined in most guidelines and literature as steatosis of more than 5% of the liver cells in the absence of excessive alcohol consumption and other known liver damage factors. Currently, NAFLD has become the most common chronic liver disease worldwide, affecting approximately 25% of adults.[1] The prevalence of NAFLD is high across all continents, with South America (31%) and the Middle East (32%) having the highest prevalence, followed by Asia (27%), the United States (24%), Europe (23%), and African having the lowest (14%),[1] which seriously threatens human health and imposes a huge burden on clinical practice and economy. The diagnosis of NAFLD is based on the following criteria, with any one of items 1–5 plus item 6 or 7 can be clinically diagnosed: (1) alcohol consumption equivalent to alcohol less than 140 g/wk for men and less than 70 g/wk for women; (2) excluding specific diseases such as viral hepatitis and drug-induced liver disease that can cause fatty liver; (3) there may be nonspecific symptoms and signs such as fatigue, indigestion, dull pain in the liver area, and hepatosplenomegaly; (4) metabolic syndrome–related components (eg, overweight and/or visceral obesity, elevated fasting blood glucose, dyslipidemia, and hypertension); (5) abnormalities in serum liver function tests; (6) B-ultrasound or CT examination: diffuse fatty liver; (7) Liver biopsy meets pathological diagnostic criteria for fatty liver disease.[2] In recent years, the view that NAFLD is a metabolic liver disease has been widely accepted.[3,4] Compared with patients without metabolic disorders, patients with obesity, elevated fasting glucose, type 2 diabetes mellitus, or other metabolic disorders are at an increased risk for advanced liver fibrosis and poor long-term prognosis. Although the histology is similar to that of alcoholic liver disease, the former exclusionary diagnosis based on alcoholic factors is not scientific. There is currently no general consensus on the definition of "metabolic health," and disagreement exists within the endocrine community over the definition of the term "metabolic syndrome," but 32 hepatologists from Europe, South America, North Africa, and the Asia-Pacific region issued a consensus statement in 2020, proposing that NAFLD be renamed metabolic-associated fatty liver disease (MAFLD), and put forward a new definition.[4] The diagnostic criteria of MAFLD are based on histological (liver biopsy), imaging, and blood biomarker evidence of hepatic fat accumulation (hepatocyte steatosis), and have one of the following three conditions: overweight/obesity, type 2 diabetes, and metabolic dysfunction. Metabolic dysfunction was defined as having at least two risk factors for metabolic abnormalities [Figure 1].[4,5] In October of the same year, the Asia-Pacific Society of Hepatology took the lead in issuing the MAFLD Management Guide,[6] followed by a number of national and regional scholars

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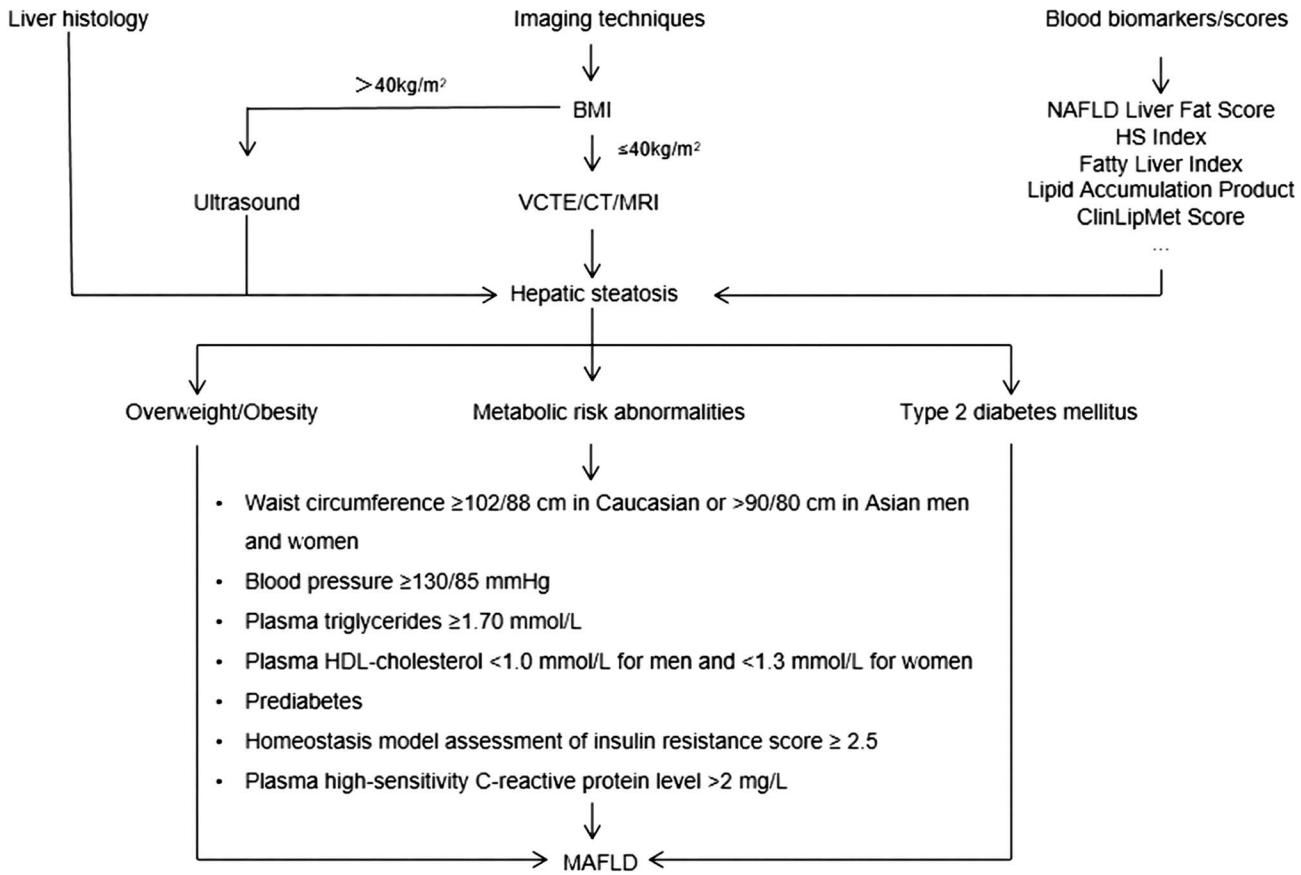

Figure 1: The diagnostic process of MAFLD. BMI: Body mass index; VCTE: Vibration-controlled transient elastography; CT: Computed tomography; MRI: Nuclear magnetic resonance Imaging; NAFLD: Nonalcoholic fatty liver disease; HS: Hepatic steatosis; HDL: High-density lipoprotein; MAFLD: Metabolism-related fatty liver disease.

Figure 2: Positions of academic organizations on the renaming of NAFLD. NAFLD: Nonalcoholic fatty liver disease; APASL: Asian Pacific Association for the Study of the Liver; MENA: Middle East and North Africa; CRP:C-reactive protein; ALEH: The Latin American Association for the Study of the Liver (Asociación Latinoamericana para el Estudio del Hígado); SSA: sub-Saharan Africa; CMA: Chinese Society of Hepatology; NASH:Non-alcoholic steatohepatitis; MAFLD: Metabolic-associated fatty liver disease; MSGH: Malaysian Society of Gastroenterology and Hepatology; CVD:Cardiovascular disease; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases.

and academic organizations issuing statements on NAFLD renaming [Figure 2].[7–12]

Recently, more than 1000 multistakeholder representatives from 134 countries and regions publicly endorsed MAFLD, and their signatures were published in *The Lancet Gastroenterology and Hepatology* in the form of an attachment to "Global Multi-stakeholder support for MAFLD definition."[13] Although MAFLD is considered to better reflect the disease characteristics of NAFLD and has better clinical application value,[14–17] it is important to note that the debate over the name change has not ceased. To date, the European Society of Hepatology and the American Society of Hepatology have not announced their statements in this regard.

Nonalcoholic fatty liver disease is often associated with overnutrition, obesity, and metabolic syndrome; however, metabolic risk factors are not necessary. The new definition of MAFLD emphasizes the role of metabolic dysfunction, and MAFLD can coexist with other liver diseases. MAFLD also increased the insulin resistance index and hypersensitive C-reactive protein based on the original five risk factors of metabolic syndrome. It can be seen that this is a "positive" diagnostic standard based on the key driving factor of metabolic dysfunction. Without considering alcohol consumption or other accompanying liver diseases, it will identify heterogeneous patient groups and high-risk patients. Many studies have confirmed this, as shown in Table 1, and renaming NAFLD to MAFLD may be a catalyst for the development of new treatments. Currently, the US Food and Drug Administration has not approved drugs for the treatment of NAFLD/MAFLD. Patients with MAFLD-related cirrhosis have a high perioperative risk, and obese patients with MAFLD should consider weight-loss surgery only if they meet the following criteria: (1) body mass index (BMI) >35 kg/m^2 in the general population, or >30 kg/m^2 in the Asian population; (2) there is no cirrhosis, or there is evidence of compensatory cirrhosis, but it is not accompanied by portal hypertension.[6]

2. Controversy over diagnostic criteria

The diagnostic process for MAFLD is complex. Two or more metabolic risk abnormalities are required for MAFLD diagnosis in nonobese patients with fatty liver disease without abnormal blood glucose metabolism. Second, hypersensitive C-reactive protein is not commonly used in metabolic risk assessment.[7] Serum aspartate transaminase and alanine transaminase are not sensitive biomarkers of liver cell injury in patients with hepatic steatosis;[18] however, studies have shown that liver enzyme elevation should be considered in the diagnostic criteria of MAFLD.[19] In addition, the proposed diagnostic criteria may be too sensitive in the general population.[20,21]

At present, ultrasound is the first choice for diagnosing fatty liver, but the sensitivity of ultrasound in diagnosing fatty liver is limited and operator dependent. When the degree of fatty liver is less than 20%, the accuracy of ultrasound decreases. In subjects with BMI greater than 40 kg/m^2, the detection performance of ultrasound is poor. As the golden standard for the diagnosis of NAFLD, pathology can not only make a definitive diagnosis but also serve as the basis for the exclusion of other liver diseases. At present, the NAFLD activity score and steatosis activity fibrosis score systems have been widely adopted in industry worldwide. However, after being renamed MAFLD, whether these "gold standards" are still applicable is challenged because of the coexistence of multiple disease modification factors, such as sex, age, diet, alcohol consumption, and genetic background. To date, the Malaysian Society of Gastroenterology and Hepatology has published 27 consensus statements on MAFLD, covering its definition, epidemiology, evaluation, and management.[12] In addition, Egyptian clinical practice guidelines for the diagnosis and management of MAFLD have been updated.[22] Moreover, the Asia Pacific Association for the Study of the Liver has provided assessment and management recommendations for general and special populations with MAFLD.[6] Comments were also made in the Middle East and north Africa regarding MAFLD terminology.[7] Furthermore, the different criteria used to define NAFLD and MAFLD can lead to a large amount of overlap in patient population identification, and confounding factors introduced by different criteria and human factors with incomplete adjustment of selection bias can also lead to differences in results, but this is not a real difference in underlying disease status. However, available evidence suggests that mortality in patients with NAFLD or MAFLD is associated with potential metabolic risk factors, not liver steatosis itself, unless it leads to advanced fibrosis.[23] More careful adjustments, such as the use of propensity score matching, may help further confirm whether there is a real association between MAFLD "itself" and

Table 1: Comparison of NAFLD and MAFLD

Authors	Study time	Study population	Prevalence (%)	Conclusion
Xia et al.[18]	June 2009 and December 2012, China	4653	FLD: 32.6 NAFLD: 26.8 AFLD/VH: 5.8 MAFLD: 28.0	MAFLD can better cover patients.
Yamamura et al.[19]	May 2017 and December 2019, Japan	765	MAFLD: 79.6 NAFLD: 70.7	MAFLD have higher liver stiffness and greater sensitivity.
Huang et al.[20]	January 2009 and December 2019, China	185	MAFLD + NAFLD: 41.1 MAFLD: 43.8 NAFLD: 4.9	MAFLD can find more patients with hepatic steatosis.
Lin et al.[21]	1988 and 1994, NHANES III	13,083	MAFLD: 29.70 NAFLD: 33.23	MAFLD had higher HOMA-IR, lipid, liver enzyme levels, and noninvasive liver fibrosis scores.

NAFLD: Non-alcoholic fatty liver disease; MAFLD: Metabolism-related fatty liver disease; FLD: Fatty liver disease; AFLD: Alcoholic fatty liver disease; VH: Viral hepatitis; NHANES III: The third National Health and Nutrition Examination Surveys; HOMA-IR: Homeostasis model assessment of insulin resistance.

all-cause mortality in the absence of advanced fibrosis. As for the diagnostic criteria of MAFLD, further research and multiparty discussion are still needed to identify the sick individual as accurately as possible and formulate a treatment and follow-up plan.

3. The influence of renaming on epidemiology

The adoption of the word MAFLD involves not only a change in name but also the definition of the disease. Worldwide epidemiological data on NAFLD are relatively complete. With the change from NAFLD to MAFLD, cases excluded by NAFLD criteria, such as alcoholism and HCV infection, were included in MAFLD, and those who met the NAFLD criteria but did not meet the MAFLD inclusion criteria were excluded from MAFLD. In clinical practice, NAFLD frequently coexists with other diseases such as viral hepatitis, whereas obesity and metabolic syndrome exacerbate the progression of alcoholic liver disease.[24,25] In the third National Health and Nutrition Examination Surveys cohort survey, the prevalence of obesity and metabolic syndrome in alcoholic liver disease patients was as high as 44.5% and 32.4%, respectively.[26] Metabolic-associated fatty liver disease associated with other liver diseases is now defined as a double (or multiple) etiological fatty liver, which further increases the prevalence of MAFLD. Studies have reported that nearly 25% of patients with MAFLD are not diagnosed with NAFLD.[27] It has been reported that a subset of patients with NAFLD develop metabolic dysfunction only after NAFLD,[28] but these patients are not classified as having MAFLD in the early stage. In addition, some patients with significant hepatic steatosis without metabolic risk, such as NAFLD in lean individuals without diabetes or metabolic disorders, would not be diagnosed with MAFLD. However, in a recent study, the atherosclerotic cardiovascular disease score of "lean" NAFLD patients was higher than that of obese NAFLD patients,[29] and the median Framingham risk score of "lean" NAFLD patients was higher than that of thin patients without NAFLD.[30] It can be seen that it is important to consider the underlying pathophysiological causes of these different but related manifestations in addition to the common factors of metabolic dysfunction, such as obesity, hypertension, or diabetes. By doing so, we can correctly identify all patients at risk and provide an appropriate level of awareness for patients and clinicians. This new definition has had a significant impact on epidemiology. How to record epidemiological data after renaming is an important problem, and we may need to conduct new research to complete it.

4. Impact on NAFLD in children

The prevalence of NAFLD has been reported to be 34.2% in obese children and adolescents and 7.6% in the general pediatric population.[31] While the incidence of MAFLD in children increases not only with increasing categories of metabolic dysfunction but also with age, liver transplantation is the only treatment option available after severe complications in children.[32] Therefore, there is an urgent need for early diagnosis and intervention of MAFLD in children and adolescents to provide opportunities for slowing the progress of the disease. Currently, the MAFLD guidelines are only applicable to adults, and there are no diagnosis or treatment specifications for children. Pediatric NAFLD is a unique entity with a more severe phenotype.[33] Although the pathogenesis of MAFLD is similar in adults and children, the pathological pathways in children, such as the effects of *de novo* lipogenesis and re-esterification of free fatty acids on hepatic fat accumulation, are still unclear.[34–36] Fatty liver is also rare in young children, and its course is determined by genetic factors such as multiple congenital metabolic diseases.[37–39] For the global nonobese MAFLD patients (8%),[31] the application of the proposed adult MAFLD standard is highly inappropriate. The Israel Defense Forces consensus report also pointed out that children younger than 10 years should not be diagnosed with metabolic syndrome.[40]

One team recommended the term pediatric fatty liver disease as the new name for fatty liver disease in children and suggested that it should be divided into the following three types: type 1 IMD (genetic metabolic disease), type 2 with abnormal metabolic function, and type 3 fatty liver with unknown cause.[41] Currently, evidence for the impact of MAFLD definition on pediatrics is limited,[41,42] and further research is needed to establish appropriate programs for screening, diagnosis, and treatment of MAFLD in children. Because of the heterogeneity of MAFLD itself, when diagnosing MAFLD in children, coexisting factors leading to other abnormal liver functions should also be evaluated (eg, Wilson disease, viral hepatitis, autoimmune hepatitis). It is necessary to develop highly sensitive and specific risk-scoring standards to determine the clinical subtypes of pediatric patients with MAFLD to achieve accurate management.

5. Controversy regarding the rationality of emphasizing "metabolism" over liver disease

MAFLD not only promotes systemic low-grade inflammation and impairs insulin sensitivity in extrahepatic tissues[43] but also increases liver insulin resistance, resulting in 30%–40% of patients progressing to nonalcoholic steatohepatitis (NASH), which eventually leads to liver cirrhosis, liver failure, and liver cancer.[44,45] However, insulin resistance, a marker of metabolic abnormalities, was not a predictor of liver mortality in MAFLD.[46] Other "metabolic" diseases can also lead to hepatic steatosis, but are not diagnosed by MAFLD. For example, patients with Wilson disease can also have a fatty liver, but the phenotype is a metabolic disease.[47] Hepatic steatosis develops before other metabolic diseases and is the initial manifestation of metabolic diseases. Merely emphasizing metabolic dysfunction will lead to an underestimation of the influence of steatosis in fatty liver diseases.[48] With the general increase in energy intake and decrease in physical activity, the prevalence of metabolic health is declining. Regardless of BMI, people with unhealthy metabolism have a higher risk of cardiovascular disease than those with a healthy metabolism.[49] However, currently, there is no consensus on the definition of "metabolic health." The disadvantage of NAFLD is that the main focus is on the liver, and the diagnosis of MAFLD is heavily dependent on related comorbidities. The naming of NAFLD has been canceled, which makes the disease naming consider coexisting diseases more carefully, but it is not beneficial to patients with severe liver diseases without obvious metabolic risk factors.[50]

Metabolic-associated fatty liver disease is a heterogeneous disease involving different pathogenic mechanisms, including genetics, gene-environment interactions, and microbiota. Metabolic disorder–driven hepatic steatosis is one such condition. MAFLD is a dynamic disease, and its pathogenic factors can change over time. Even if only lipids, carbohydrates, and fat metabolism are considered, they still need to be classified into etiological categories, and these differences cannot be covered by a simple name change.[51] Therefore, various phenotypic component analyses

are needed to reflect the etiology of the disease and guide the formulation of clinical treatment and prognosis.

6. Diagnosis and treatment challenges brought by dual/multiple etiologies

As a manifestation of multisystem metabolic dysfunction involving the liver, MAFLD has certain heterogeneity in its pathogenesis, clinical manifestations, pathological changes, and natural outcome. With the increasing global prevalence of overweight or obesity, type 2 diabetes, and other metabolic abnormalities, and the decline in mortality from viral hepatitis after effective drug treatment, the possibility of MAFLD coexisting with other liver diseases is increasing.[15] Coexistence of MAFLD with drug-induced liver injury, viral hepatitis, and excessive alcohol intake has been demonstrated in clinical practice.[25,52–54] Patients with other liver diseases who meet the diagnostic criteria for MAFLD are defined as having fatty liver with a dual (or more) etiology.[4] However, the etiology of fatty liver is unclear, and MAFLD is highly heterogeneous because of the coexistence of multiple risk factors. Disease heterogeneity poses great challenges to the development of accurate diagnosis, staging, noninvasive diagnosis, treatment plan formulation, efficacy evaluation, and other aspects.

One of the most important barriers to the selection of reliable biomarkers and diagnostic methods is the heterogeneity of the disease and the diversity of histopathology, which were not further clarified in the proposed name change. In recent years, many new scoring systems have been developed for NAFLD or MAFLD with different diagnostic targets, including NASH,[55] NASH liver fibrosis,[56–60] significant fibrosis,[61,62] advanced fibrosis or compensated cirrhosis,[63,64] and high-risk varicose veins;[65–67] the application of these scoring systems in clinical practice will also be challenged under the new name MAFLD.[68] Similarly, the development of treatment regimens faces significant challenges due to the multifaceted nature of disease targets, ambiguity and randomness of study end points, and high incidence of "placebo effects."[69]

7. Impact on drug discovery

Steatohepatitis is not only a driving factor for the progression and clinical outcome of liver fibrosis but also a manifestation of disease activity. Solving steatohepatitis is a treatment objective.[70–72] Nonalcoholic steatohepatitis is regarded as the only legitimate medical treatment segment of NAFLD in the guidance of regulators,[73] and new biomarkers and noninvasive diagnostics are also being developed and verified. To regulate the development of NASH drugs more effectively, both the US Food and Drug Administration and the European Drug Administration have issued relevant guidance statements; previous research and development of new NAFLD drugs focused on NASH, and treatment end points emphasized NASH remission without exacerbation of liver fibrosis and/or reversal of liver fibrosis without exacerbation of NASH. These views have been challenged to varying degrees by the renaming.[74] Nonalcoholic steatohepatitis is an important descriptive entity; it would be inappropriate to treat MAFLD in the same manner as other chronic liver diseases with some degree of activity and fibrotic stages, and no longer use the classifications of NASH and non-NASH.

There are two types of end points in clinical trials of new NASH drugs: (1) the evaluation of liver fat content and inflammation/fibrosis using noninvasive indicators, such as nuclear magnetic resonance imaging and liver stiffness measurement, and (2) histological improvement, including the reduction of NASH fibrosis and the improvement of NASH score. "NASH remission without exacerbation of liver fibrosis" will no longer be the end point of new drug development for MAFLD. A significant reduction in the degree of liver inflammation and injury is more likely to reflect the reversal of liver fibrosis than a decrease in NAFLD activity score, and drugs that do not significantly improve liver fibrosis will be difficult to approve for routine treatment of MAFLD. Considering that MAFLD often coexists with many other chronic diseases, the development of new drugs for MAFLD also needs to consider the interaction of combined drugs and heart and kidney safety. The evaluation criteria for the clinical efficacy of drugs also need to be further studied.

No drugs have been approved by regulatory agencies for NAFLD or MAFLD. However, before that, some drugs were recognized by the International Liver Association and expert working groups, such as pioglitazone[75–78] and vitamin E.[75,79,80] Because of the change in diagnostic criteria brought about by the name change, the role of these drugs remains to be studied, rendering it a catalyst for the development of new drugs. However, currently, the efficacy of the new drugs for MAFLD is lower than expected in clinical trials, which may be related to the complex pathophysiological mechanism of MAFLD, which is a liver disease associated with obesity, diabetes, and metabolic dysfunction. In addition to reversing fibrosis, the ideal treatment should have metabolic and cardiovascular benefits without increasing body fat or reducing muscle content. To this end, combination drug treatment strategies that act on multiple disease drivers simultaneously, patient stratification based on drug mechanism of action, standardization of lifestyle interventions across treatment groups, and some innovative clinical trial designs may contribute to accelerated drug development. Further prospective studies are needed to type the disease and stratify patients at risk to provide effective treatment for patients with MAFLD as soon as possible.

8. Impact on clinical trials

The current trial recruitment is based on histological grading and staging, and many different pathogenic causes may lead to the same histological phenotype. The lack of analysis of the main causes is a key issue in clinical research. Recruitment will be significantly more difficult with detailed stratification and inclusion of patients based on disease drivers in accordance with the MAFLD diagnostic criteria. Groups with excessive drinking combined with HBV infection were included in the diagnosis of MAFLD. New drug development plans must take into account the coexistence of such groups of liver diseases to improve the efficiency of drug development and avoid disconnection between new drugs and clinical practice. Although significant efforts have been made in NASH drug development and clinical trials, treatment is usually limited to lifestyle changes.[81,82]

The reason for the repeated failure of clinical trials lies in the heterogeneity of the pathogenesis, clinical manifestations, and subsequent determinants of NAFLD progression. Further advances in understanding the pathophysiology of the disease will point the way for subsequent research. To date, patients in anti-NAFLD clinical trials have been excluded from significant alcohol intake, and changing the name from NAFLD to MAFLD

would put the current phase 2b and 3 advanced drug trials at risk. Metabolic-associated fatty liver disease emphasizes the role of metabolic factors; however, metabolic heterogeneity is not considered in the design of most NAFLD standard clinical trials. After renaming NAFLD as MAFLD, this method can reflect obesity-related and diet-induced MAFLD, and other causes of MAFLD need to be modeled separately *in vitro* to allow drug development to be tailored to the underlying causes of this disease subtype. As suggested by Eslam et al.,[3] a new clinical trial design requires stratified patient composition based on the etiology of MAFLD.

Most established *in vitro* models of NAFLD rely on short-term fatty acid exposure and use fat accumulation as a phenotypic baseline.[83] This general method is no longer applicable to MAFLD, which is a seemingly general disease. It is necessary to have a deeper understanding of the pathogenesis of fatty liver to promote the development of anti-MAFLD drugs by layering patients, so that each subgroup can benefit from different pharmacological interventions.[84] Therefore, in early preclinical disease modeling and drug testing, there is a need to develop human-based *in vitro* models that accurately reflect the different disease subgroups of MAFLD. In addition to cell sources and *in vitro* disease triggers, each cell culture system has its own specific advantages and limitations when model exit *in vitro*,[85] and these characteristics should be incorporated into the design to reduce failure in later clinical studies. The preparation of a NASH animal model, which presents with the characteristics of people and is easy to operate, requires further exploration. It is believed that future research will enable us to further describe and subdivide the phenotype of the disease and its drivers to design a more reasonable clinical diagnosis, treatment plan, and patient management plan.

9. Knowledge dissemination to raise awareness of liver disease

In primary and secondary care, MAFLD remains an unrecognized and undiagnosed disease,[86–88] resulting in a low overall public health response to MAFLD.[89] There is consistent evidence that individuals with a low level of health knowledge show improvement through communication and other interventions.[90,91] However, the change in disease naming not only has a profound impact on patients but also creates unnecessary clinical confusion among healthcare professionals, such as cardiologists, diabetologists, and primary care providers involved in the care of patients with NAFLD. At present, while carrying out better risk stratification, early diagnosis, and management of MAFLD, it is also necessary to strengthen the knowledge dissemination to reduce the public health burden caused by the disease. Regulations are needed to ensure that patients with MAFLD are properly triaged and managed, with limited health systems and resources at all levels.

10. Conclusions

The name change from NAFLD to MAFLD reflects that the essential attribute of NAFLD is metabolic liver disease, and it also pays attention to the harmful effects of NAFLD on metabolic-related diseases outside the liver, which is of great significance for disease understanding, prevention, and improvement of prognosis. However, some problems remain to be resolved. Fatty liver disease is clinically heterogeneous, not only related to metabolic and alcohol causes but also to idiopathic/cryptogenic fatty liver disease. Nonalcoholic fatty liver disease is an exclusive diagnosis, which confuses stakeholders and makes it difficult to convey information, thus affecting the understanding of the disease by doctors and patients in other disciplines, leading to stigmatization. MAFLD reflects the related risk factors more accurately and positively than NAFLD, but the term is still vague, because it abandons NASH and weakens the liver disease stratification of NAFLD. The definition of "metabolism" in MAFLD does not eliminate the ambiguity of etiological diagnosis, and there is currently a lack of consensus on the concept of metabolic health. The diversity of characteristics makes the treatment target unclear, the evaluation of efficacy complex, and the direction of new drug research and development difficult to discern. Changing the name does not address key needs that remain unmet in this area. The research by Kim et al.[29] is commendable, and the renaming is of great significance, but how to better define and classify remains a major problem that needs to be solved. Given the extremely high prevalence of this problem, it is essential to raise awareness among patients and care providers about the existence of "fatty liver" and careful health assessment of patients and long-term medical plans to reduce the risk of future adverse outcomes, regardless of the diagnostic criteria of NAFLD/MAFLD. It is expected that there will be large, multicenter, prospective cohort studies in the future to guide the formulation of a more accurate definition, improvement of diagnostic criteria, clinical subclassification, treatment principles and efficacy evaluation, drug research and development, clinical trials, and other aspects.

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Author Contributions

Minghui Zeng, Liang Xu, and Yuqiang Mi designed the study. Minghui Zeng, Yuqin Li, and Lin Chen drafted the manuscript. Yuqiang Mi and Liang Xu made critical revision. All authors read and approved the final manuscript.

Conflicts of Interest

None.

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