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Editorial Board Member of *World Journal of Hepatology*, Igor Skrypnyk, MD, MDS, PhD, Professor, Internal Medicine #1, Poltava State Medical University, Poltava 36011, Ukraine. inskrypnyk@gmail.com

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EDITORIAL

Predictive value of serum alanine aminotransferase for fatty liver associated with metabolic dysfunction

Wen-Xiu Liu, Lei Liu

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Wen-Xiu Liu, Lei Liu, State Key Laboratory of Oral Diseases, National Center for Stomatology, National Clinical Research Center for Oral Diseases, Department of Oral and Maxillofacial Surgery, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, Sichuan Province, China

Corresponding author: Lei Liu, MD, PhD, Academic Editor, Chief, Professor, Surgeon, State Key Laboratory of Oral Diseases, National Center for Stomatology, National Clinical Research Center for Oral Diseases, Department of Oral and Maxillofacial Surgery, West China Hospital of Stomatology, Sichuan University, No. 14 Section 3, Renminnan Road, Chengdu 610041, Sichuan Province, China. drliulei@163.com

Abstract

In this editorial, we offer commentary on the article published by Chen *et al* in a recent issue of the *World Journal of Gastroenterology* (2024; 30: 1346-1357). The study highlights a noteworthy association between persistently elevated, yet high-normal levels of alanine transaminase (ALT) and an escalated cumulative risk of developing metabolic dysfunction-associated fatty liver disease (MAFLD). MAFLD has emerged as a globally prevalent chronic liver condition, whose incidence is steadily rising in parallel with improvements in living standards. Left unchecked, MAFLD can progress from hepatic steatosis to liver fibrosis, cirrhosis, and even hepatocellular carcinoma, underscoring the importance of early screening and diagnosis. ALT is widely recognized as a reliable biomarker for assessing the extent of hepatocellular damage. While ALT levels demonstrate a significant correlation with the severity of fatty liver disease, they lack specificity. The article by Chen *et al* contributes to our understanding of the development of MAFLD by investigating the long-term implications of high-normal ALT levels. Their findings suggest that sustained elevation within the normal range is linked to an increased likelihood of developing MAFLD, emphasizing the need for closer monitoring and potential intervention in such cases.

Key Words: Metabolic dysfunction-associated fatty liver disease; Alanine aminotransferase; Upper reference limits; Fibrosis; Metabolic dysfunction-associated steatohepatitis; Cirrhosis

Core Tip: Elevated alanine aminotransferase (ALT) levels are strongly associated with an increased risk of metabolic dysfunction-associated fatty liver disease (MAFLD). Therefore, ALT can serve as a valuable biomarker for predicting both the occurrence and prognosis of MAFLD, making it a significant tool in assessing liver health.

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INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD), formerly recognized as non-alcoholic fatty liver disease, has gained increasing attention in recent years due to advancements in understanding its pathogenesis and the alarming rise in its prevalence. In 2020, the International Consensus Panel issued a consensus, outlining new diagnostic criteria for MAFLD[1]. The diagnosis of MAFLD can be established through liver biopsy histological examination, imaging examination, or blood biomarker analysis indicating the presence of fatty liver, along with meeting at least one of the following criteria: Overweight/obesity, type 2 diabetes mellitus (T2DM), or evidence of metabolic dysfunction[2]. MAFLD encompasses a broad spectrum of liver conditions, ranging from simple steatosis to more severe manifestations such as metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and even hepatocellular carcinoma. This diverse range of pathologies affects over one-third of the global population, with its escalating prevalence attributed to the widespread occurrence of T2DM, hypertension, obesity, and hyperlipidemia[3]. MASH, considered a progressive form of MAFLD, is characterized by hepatic steatosis, hepatocyte swelling, and lobular inflammation. This condition leads to the accumulation of fat in the liver, resulting in inflammation and hepatocyte damage. As the disease progresses, hepatic stellate cells become activated, initiating excessive collagen production and ultimately leading to liver fibrosis. This fibrotic process is a significant contributor to increased mortality and associated complications in MAFLD, and the severity of liver fibrosis serves as a critical determinant of long-term prognosis for MAFLD patients[4,5]. Furthermore, MAFLD is associated with an increased risk of metabolic syndrome, T2DM, atherosclerotic disease, and peripheral vascular disease. Notably, the prevalence and incidence of malignant tumors, including liver cancer, breast cancer, lung cancer, and rectal cancer, are higher among MAFLD patients compared to non-MAFLD individuals, imposing a significant economic burden on both affected individuals and society[6,7].

PATHOGENESIS AND INTERVENTION STRATEGIES

The pathogenesis of MAFLD is highly intricate, with a close interplay between genetic predisposition, environmental exposures, and lifestyle choices. In 1998, Day *et al*[8] first introduced the "second-hit" hypothesis, which emphasized factors like insulin resistance, oxidative stress, inflammation, and disrupted lipid metabolism as key players. However, as research has progressed, the "multi-hit" theory has gained traction[9]. This theory posits that when hepatocytes accumulate significant lipids and exhibit insulin resistance, a cascade of metabolic perturbations ensues, with genetic susceptibility and insulin resistance being among the multiple cumulative factors driving the onset and progression of MAFLD. Concurrently, genetic variants like PNPLA3, unhealthy dietary patterns rich in fat and calories, and sedentary lifestyles have emerged as notable risk factors for the development of this disease[10].

Lifestyle interventions encompassing dietary modifications, energy restriction, and regular physical activity are presently advocated as effective measures for treating MAFLD. Additionally, medications commonly used to treat obesity, such as orlistat[11], and those used in the management of T2DM, including semaglutide[12] and pioglitazone [13], are believed to confer benefits for patients with MAFLD. However, the majority of these therapeutic agents are still undergoing clinical trials, necessitating further research to substantiate their efficacy. Bariatric surgery emerges as an alternative treatment option for obese individuals with MAFLD. Nevertheless, concerns arise from studies indicating potential serious complications associated with this surgical procedure, necessitating further investigation into its clinical efficacy and safety profile[14].

DETECTION AND DIAGNOSIS

Patients with MAFLD typically experience an insidious onset, slow progression, and a lack of pronounced symptoms during the early stages. It is only when liver function becomes severely compromised, or when cirrhosis or liver cancer develops, that the condition garners widespread attention. This delayed recognition significantly impacts the diagnosis, treatment, and prognosis of the disease. Early detection and diagnosis of fatty liver, coupled with the implementation of appropriate intervention measures, can have a profound effect in delaying or even reversing disease progression. Therefore, screening and early diagnosis of MAFLD, as well as intervention for associated risk factors, are crucial for

improving the prognosis of this debilitating condition.

Currently, the diagnosis of MAFLD predominantly relies on the identification of hepatic steatosis through blood tests, imaging studies, or liver histology. Although liver biopsy serves as the gold standard for diagnosing MAFLD due to its invasive nature, the limited sample size can lead to diagnostic deviations and inaccurate severity assessments. Additionally, this method is associated with various potential complications, such as bleeding, abdominal discomfort, and pain, which often render it unacceptable to patients[15]. Ultrasound examination, particularly ultrasound transient elastography technology, is widely utilized owing to its safety, affordability, convenience, non-invasiveness, and quantitative detection capabilities for liver tissue. This technology offers superior prediction of liver steatosis[16,17]. However, it exhibits reduced sensitivity in obese patients, limiting its applicability for large-scale population screening. Magnetic resonance spectroscopy provides quantitative assessment of liver fat content but is costly and requires specialized software, posing challenges for its widespread clinical adoption[18]. Therefore, there is an urgent need to investigate biomarkers that can facilitate early diagnosis and effective monitoring of MAFLD disease progression.

ALT LEVELS AND MAFLD RISK

While the new expert consensus has acknowledged the importance of blood biomarkers in diagnosing MAFLD, there remains a notable gap in the availability of effective biomarkers for clinical use. Prior research has pointed to the predictive potential of cytokeratin 18, alanine aminotransferase (ALT), and aspartate aminotransferase in identifying MAFLD[19]. Of these, ALT holds significant weight as a key indicator of liver function, reflecting both liver inflammation and injury across a range of chronic liver diseases. Typically, serum ALT levels are low in healthy individuals but increase markedly in response to hepatocyte apoptosis and injury[20,21]. Historically, higher ALT values have been strongly correlated with an elevated risk of MAFLD. However, ALT levels alone can be nonspecific in MAFLD diagnosis, with approximately 25% of patients presenting with normal ALT levels[22]. Clinically, many physicians rely on ALT level changes to assess MAFLD risk, a strategy that may overlook affected patients with persistently normal ALT. Numerous studies have demonstrated that liver injury can occur even in the presence of normal ALT levels, with a concerning 37.5%-59% of MAFLD patients with normal ALT being diagnosed with MASH or advanced fibrosis[23]. Verma *et al*[24] reported that while patients with normal ALT levels exhibited a significantly lower rate of MASH compared to those with elevated ALT, there was no marked difference in cirrhosis rates between the two groups.

The study by Chen *et al*[25], presents intriguing findings regarding the relationship between ALT levels and the development of MAFLD. After analyzing clinical data from 3553 Chinese adults who underwent health examinations spanning three consecutive years from January 2017 to December 2019, the researchers categorized the subjects into three groups based on their ALT levels: Low-normal ALT, high-normal ALT (hALT), and abnormal ALT, using the standard ALT range of 0-40 U/L as a reference. Notably, the study revealed a direct correlation between the incidence of MAFLD and cumulative excess normal ALT (ehALT), indicating that individuals with persistently high-normal ALT levels face an elevated cumulative risk of developing MAFLD.

MAFLD has emerged as a significant public health concern, and this study offers valuable insights into predicting incident cases by examining repeated measurements of high-normal ALT levels. Going forward, identifying and addressing these elevated ALT levels through lifestyle modifications can lead to improvements and prevent the onset of MAFLD. However, it raises the question of whether we should reconsider the upper reference limits (URLs) for ALT levels. Lowering these URLs could potentially aid in the early detection of MAFLD and enhance our ability to predict its progression. Some experts have suggested new URLs of 42 U/L for men and 30 U/L for women, which are approximately 30% lower than the current recommendations of the International Federation of Clinical Chemistry. While these lower limits may increase sensitivity and improve the detection of steatosis and significant fibrosis in individuals with metabolic abnormalities, they also come with limitations in accuracy[26]. Nonetheless, this remains an intriguing area for future research.

CONCLUSION

MAFLD comprises a range of liver diseases whose prevalence is escalating alongside improvements in living standards. The screening and early diagnosis of MAFLD are crucial. ALT, a significant biomarker of liver function, exhibits a strong correlation with the elevated risk of MAFLD. Furthermore, persistently high-normal ALT levels are associated with an increased cumulative risk of developing new-onset MAFLD. In summary, ALT could serve as a valuable predictor of both the occurrence and prognosis of MAFLD.

FOOTNOTES

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Country of origin: China

ORCID number: Wen-Xiu Liu 0009-0008-0019-8914; Lei Liu 0000-0001-5309-1979.

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