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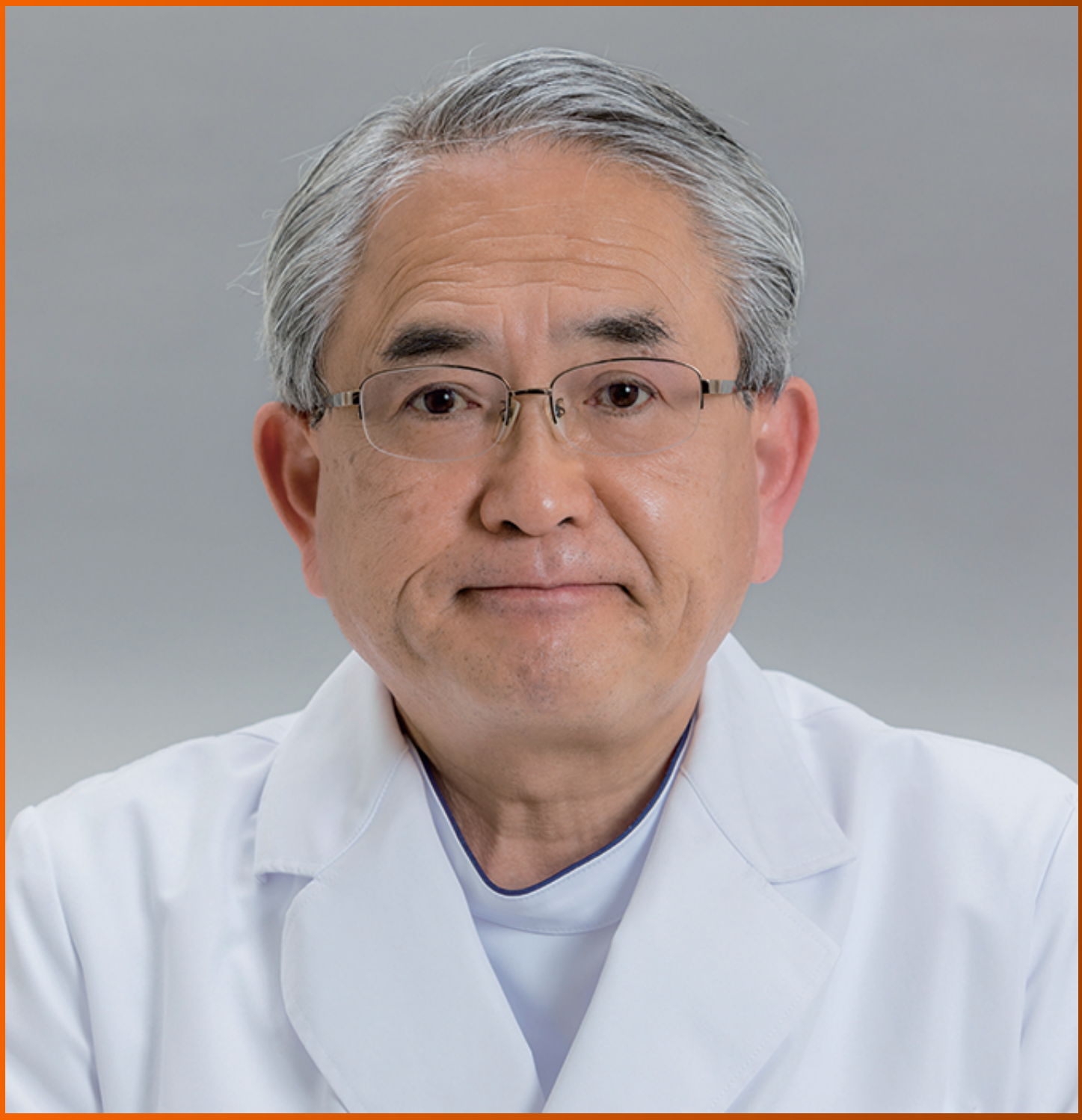

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EDITORIAL

Alanine aminotransferase as a risk marker for new-onset metabolic dysfunction-associated fatty liver disease

Di Wang, Bing-Yan Zhou, Lei Xiang, Xu-Yong Chen, Jie-Xiong Feng

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Abstract

In this editorial, we comment on the article by Chen *et al*. Metabolic dysfunction-associated fatty liver disease (MAFLD) is a global public health burden whose incidence has risen concurrently with overweight and obesity. Given its detrimental health impact, early identification of at-risk individuals is crucial. MAFLD diagnosis is based on evidence of hepatic steatosis indicated by liver biopsy, imaging, or blood biomarkers, and one of the following conditions: Overweight/obesity, type 2 diabetes mellitus, or metabolic dysregulation. However, in large-scale epidemiological studies, liver biopsies are not feasible. The application of techniques such as ultrasonography, computed tomography, magnetic resonance imaging, and magnetic resonance spectroscopy is restricted by their limited sensitivity, low effectiveness, high costs, and need for specialized software. Blood biomarkers offer several advantages, particularly in large-scale epidemiological studies or clinical scenarios where traditional imaging techniques are impractical. Analysis of cumulative effects of excess high-normal blood alanine aminotransferase (ALT) levels of blood ALT levels could facilitate identification of at-risk patients who might not be detected through conventional imaging methods. Accordingly, investigating the utility of blood biomarkers in MAFLD should enhance early detection and monitoring, enabling timely inter-vention and management and improving patient outcomes.

Key Words: Nonalcoholic fatty liver disease; Metabolic dysfunction-associated fatty liver disease; Alanine aminotransferase; Screening; Risk marker

Core Tip: This editorial discusses the article by Chen *et al* regarding the association between high-normal alanine aminotransferase (ALT) levels and the onset of metabolic dysfunction-associated fatty liver disease (MAFLD) in China. As an indicator of liver function, ALT could be considered a marker of the presence of MAFLD. Therefore, tracking cumulative ALT levels could enhance early MAFLD detection. Improved detection through ALT tracking could enable timely intervention, thereby enhancing overall health outcomes for individuals at risk of developing this increasingly common liver condition.

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INTRODUCTION

The concept of nonalcoholic steatohepatitis (NASH) was first introduced by Ludwig *et al*[1] at the Mayo Clinic in 1980. It was broadened and described as nonalcoholic fatty liver disease (NAFLD) in 2002, encompassing a wider spectrum of liver conditions characterized by excessive fat accumulation not due to alcohol intake[2]. However, this term may have led to the misunderstanding that NAFLD is a benign and stable condition, resulting in a lack of in-depth research into techniques for the diagnosis and evaluation of this disease. Metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed in 2020 as an updated name for NAFLD[3]. This nomenclature change better reflects the metabolic dysfunction that is linked to this prevalent liver disease and not present in other liver diseases. MAFLD has become a global public health challenge in the past two decades. Epidemiological studies estimate that MAFLD affects more than one-quarter of the adult population in both developed and developing countries worldwide[4,5]. Its prevalence rate was 29.2% in China[6], 30% in the United States[7], and 23.7% during 2011-2015 in Europe[8]. The incidence of MAFLD has been increasing. Specifically, a meta-analysis has indicated a pooled estimated incidence rate of MAFLD of 52.34 per 1000 individuals in China and Japan, with a 95% confidence interval ranging from 28.31 to 96.77, underlining the growing prevalence of the condition[8].

MAFLD includes a histological spectrum of liver conditions and is characterized by an initial accumulation of fat in hepatocytes. As the condition advances, inflammatory processes ensue, culminating in liver fibrosis and subsequent scarring, potentially escalating to severe hepatic damage that manifests as cirrhosis and hepatocellular carcinoma (HCC)[3]. MAFLD is not merely a liver condition, but a systemic disease associated with metabolic disorders including type 2 diabetes mellitus, hypertension, and dyslipidemia, contributing to increased susceptibility to cardiovascular diseases. Evidence has been reported regarding the extrahepatic involvement of MAFLD, *e.g.*, in chronic kidney disease, hypothyroidism, polycystic ovarian syndrome, obstructive sleep apnea, and osteoporosis[9-11]. As the disease progresses, outcomes may include liver failure, necessitating liver transplantation, or death of the patient. In sum, MAFLD is a silent disease, with vague or no symptoms, that poses a significant threat to public health and individuals' quality of life. Early detection of MAFLD prior to the onset of symptoms is pivotal to enable timely intervention, which could halt the progression of the disease, reverse mild cases, and possibly ameliorate NASH.

DIAGNOSIS AND SCREENING OF MAFLD

The diagnostic criteria for MAFLD are based on histological (liver biopsy), radiological, and blood biomarker evidence of hepatic steatosis, combined with at least one of the following three conditions: overweight/obesity, type 2 diabetes, or the presence of metabolic dysfunction[3]. The characteristic of MAFLD necessitates accurate diagnostic techniques for effective management and treatment.

Liver biopsy remains the gold standard for diagnosing and assessing the severity of MAFLD, although its invasive nature poses risks such as bleeding, infection, and pain. Moreover, the procedure's reliance on small tissue samples can introduce diagnostic bias and may not accurately reflect the overall condition of the liver[12]. In the diagnosis of MAFLD, imaging modalities are widely utilized. Commonly employed imaging techniques include ultrasonography (US), vibration-controlled transient elastography (VCTE), computed tomography (CT), and magnetic resonance imaging (MRI). although US is the most widely used first-line diagnostic modality, its effectiveness is hampered by operator dependency and technical limitations, especially in mild cases or in patients with high body mass index (BMI). The diagnostic sensitivity of US markedly decreases to 60% for steatosis levels under 30% or in individuals with a BMI exceeding 40 kg/m^2, in contrast to a 93% sensitivity for steatosis levels above 30%[13]. VCTE uses ultrasound to estimate liver fibrosis by measuring liver stiffness based on the speed of a mechanically induced shear wave in the liver tissue. The controlled attenuation parameter exhibited an area under the receiver operating characteristic curve of 0.87 in diagnosing patients with steatosis[14]. CT offers only slight improvements in sensitivity when detecting mild cases of steatosis, posing challenges in early-stage disease identification. Additionally, this modality involves higher financial costs to patients and healthcare systems, as well as increased exposure to radiation. MRI and magnetic resonance spectroscopy (MRS) are capable of accurately identifying hepatic steatosis when it exceeds a 5% threshold, and MRI-proton density fat fraction

can be used for the quantification of hepatic steatosis. However, this modality incurs significant costs as well, and MRS remains predominantly accessible only at academic medical institutions[15]. Blood biomarkers offer the advantages of non-invasiveness, ease of repeat measurement, and potential cost-effectiveness in assessing the condition and progression of MAFLD. Commonly used chemistries include liver enzymes, steatosis indicators, fibrosis markers, inflammatory markers, and metabolic markers. Liver enzymes demonstrate inadequate performance in diagnosing the prevalence of MAFLD, given nearly 78% of patients present with normal levels in blood tests[8,16]. Studies also suggest the potential use of the Fibrosis 4 Index score for risk stratification and the significance of serum osteocalcin levels as an independent risk factor for MAFLD in patients with type 2 diabetes mellitus[17-19].

Using a combination of clinical findings, imaging, and biochemical markers, non-invasive algorithms were developed to estimate the likelihood of hepatic steatosis. The most commonly used diagnostic models are fatty liver index (FLI), hepatic steatosis index, NAFLD-liver fat score (LFS), Steato Text (ST), and visceral adiposity index. Each model utilizes specific parameters to provide a reliable assessment of liver fat content but not the severity, offering a different balance between complexity, cost, availability of tests, and integration of metabolic factors. The choice of which algorithm to use depends on the specific clinical setting, the population diversity, and the resources available for testing. Among these models, FLI, HIS, and NAFLD-LFS estimate the presence of steatosis with an emphasis on liver enzymes and simple anthropometric measures. NAFLD-LFS and ST include broader metabolic markers. ST involves the most complex array of parameters, making it potentially more precise but less practical for routine screening. A study evaluating the efficacy of various algorithms for detecting MAFLD, using the third national health and nutrition examination survey data, demonstrated that NAFLD-LFS estimated the prevalence of MAFLD most accurately, while FLI had the highest diagnostic accuracy[20]. The use of FLI, NAFLD-LFS, and ST is recommended by the European association for the study of the liver (EASL) clinical practice, the national institute for health and care excellence (NICE) guidelines, and the Asia-pacific working party on NAFLD guidelines[21-24].

The identification of MAFLD in its early stages is crucial for early interventions that can lead to improved liver function, reduced progression, and an overall enhancement in patient health and quality of life. Moreover, early management extends beyond liver health, potentially reducing the risk of cardiovascular diseases, type 2 diabetes, and other metabolic disorders. Currently, there is an ongoing debate on screening guidelines for identifying MAFLD in the general population. The American Association for the Study of Liver Disease (AASLD) does not recommend routine screening for NAFLD among asymptomatic populations, even if they are high-risk[12]. In contrast, the EASL guidelines recommended routine screening for MAFLD with liver enzymes and/or United States in all patients with obesity or metabolic disorders. Screening is recommended for individuals with persistently elevated liver enzymes[21,25]. The NICE guidelines and Asia-pacific working party on NAFLD guidelines recommended screening for high-risk groups with obesity and type 2 diabetes mellitus. United States, rather than liver enzymes, is advised as the preferred screening modality[22,23]. The lack of a universal consensus on screening may reflect the imprecision of existing detection tools.

THE SIGNIFICANCE OF ALANINE AMINOTRANSFERASE ELEVATION AS A BIOMARKER

The ideal biomarker is an objective measure that reflects normal physiologic processes or pathogenic changes indicative of disease. Alanine aminotransferase (ALT) has long been utilized as a biomarker of liver health. ALT catalyzes the conversion of L-alanine and 2-oxoglutarate into pyruvate and L-glutamate, within liver cells, for cellular energy production. This process involves the subsequent conversion of pyruvate to lactate, during which NADH is oxidized to NAD[16]. When liver cells are subject to insults, they undergo necrosis or apoptosis, releasing their contents into the bloodstream. These contents can be detected through blood tests. Therefore, routine monitoring of ALT levels in the bloodstream can provide valuable information about liver health.

Elevated ALT levels are indicative of liver injury or damage, making it an essential factor in diagnosing and monitoring the progression of liver diseases and conditions. The degree of ALT elevation can sometimes reflect the severity of liver damage. Very high levels of ALT typically suggest acute liver damage, while chronic liver conditions might be associated with mild to moderate elevation of ALT levels[26-30]. Nonetheless, ALT level does not correlate well with the severity of chronic liver disease as observed in biopsies[16]. Elevated levels of ALT have been reported to be associated with various liver disease outcomes including hepatitis, HCC, and MAFLD. A delayed increase in ALT levels post-surgery is associated with early mortality in patients with hepatitis B virus-related HCC[31]. In NAFLD and NASH, increased levels of ALT are the most prevalent abnormal liver indicator compared with elevations in alkaline phosphatase and γ-glutamyltransferase, which occur less frequently[32]. It has also been reported that NAFLD is responsible for the asymptomatic increase in aminotransferase levels in as many as 90% of cases[33]. Thus, ALT acts as an important diagnostic and prognostic marker in liver diseases.

ALT can also serve as a screening tool to identify individuals at high risk for liver diseases. However, there is still no universal consensus on the normal range of ALT levels[34,35]. The AASLD recommended lowering the upper limit of normal (ULN) for ALT to address the issue of undiagnosed conditions and enhance early detection of liver disease. It proposed that the ULN for ALT should be 35 U/L for males and 25 U/L for females, while EASL recommended a ULN of 40 U/L for ALT, irrespective of gender[36,37]. The trend is still to lower ULNs to enhance the sensitivity of ALT in detecting liver disease. Normal ALT levels are typically determined based on population studies and are intended to serve as a general guideline. However, these normal ranges may not accurately reflect optimal liver function for every individual, especially those with underlying health conditions such as MAFLD.

ALT can be utilized as a dynamic marker with significant value in the prevention and treatment of liver diseases. In patients diagnosed with MAFLD, periodic ALT testing can represent a practical tool for monitoring disease progression

or stability[38]. Changes in ALT levels may indicate exacerbation or amelioration of liver inflammation, guiding the modification of treatment protocols and lifestyle interventions. A significant decrease in ALT levels after initiating therapy could suggest a positive response, whereas stable or increasing levels might indicate a need for alternative treatments. For MAFLD patients with elevated ALT, targeted dietary advice, such as reducing intake of saturated fats and sugars, and recommendations for physical activity can be personalized based on ALT trends[39,40]. Discussing changes in ALT levels during clinical visits can encourage patients to adhere more closely to prescribed therapeutic regimens and lifestyle changes. For patients on medications that might influence liver enzymes or those being treated for MAFLD with drugs, ALT screening helps monitor potential drug-induced liver injury or confirm therapeutic effects, respectively[41]. In sum, regular ALT measurements can facilitate integrated management of metabolic conditions.

THE ASSOCIATION BETWEEN ALT ELEVATION AND MAFLD

The relationship between ALT elevation and the occurrence or progression of MAFLD is mutual and bidirectional. The increased risk of elevated ALT levels in MAFLD may be attributed to long-term excessive fat accumulation within liver cells. Dysregulated lipid metabolism leads to uncontrolled lipolysis, lipogenesis, and fatty acid oxidation, creating a lipotoxic environment that ultimately promotes liver cell death (*via* necrosis, apoptosis, or pyroptosis)[42-44]. Lipid droplet remodeling and lipotoxicity involve organellar dysfunction, including endoplasmic reticulum stress, mitochondrial dysfunction, lysosomal permeabilization, impaired autophagy, extracellular vesicle release, and hypoxia [45]. Additionally, liver cell damage induces an inflammatory response which in turn accelerates liver injury[46]. Thus, ALT enters the bloodstream from the damaged hepatocytes, resulting in increased blood ALT levels. The long-term dynamic elevation of ALT levels may stimulate lipogenesis, which is activated by impaired cellular redox potential and/or hyperinsulinemia, promoting the occurrence and development of MAFLD[47].

There is evidence that elevated ALT, even within the normal range, correlates with increased liver fat accumulation. Previous studies report that 30%-60% of patients with MAFLD have normal ALT levels, according to general criteria, which suggests that the current thresholds may not be sensitive enough to detect subtle liver abnormalities in certain populations[16,29,48]. A high ALT level that falls within the normal range for the general population may still be considered abnormal for a particular individual based on their health status and medical history. Ma *et al*[49] reported that 25% of Chinese individuals diagnosed with NAFLD and 19% of those with NASH exhibit normal ALT levels. The study by Chen *et al*[50] that is discussed in this Editorial reported a higher rate, finding that 83% of MAFLD patients had normal ALT levels. The normal range of ALT in MAFLD remains debatable. A meta-analysis of 86 studies analyzing 526641 individuals proposed a validated ULN of the ALT level in the Asian population of 37 U/L for males and 31 U/L for females[51]. The Liver-Bible-2020 cohort study suggests an upper threshold of 35 U/L for males and 22 U/L for females[52]. For pediatric patients, a previous study demonstrated that serum transaminase levels are significantly correlated with age and gender, and identified ALT level thresholds for screening NAFLD. The ALT levels had the highest accuracy and specificity at the 92.58th percentile for male pediatric patients and the 92.07th percentile for female pediatric patients with NAFLD[53].

Serum ALT levels vary by demographic characteristics such as age, gender, BMI, and genetic background. ALT levels show age-related trends and are influenced by hormonal changes during menopause, which makes their clinical interpretation complex. Research has indicated that ALT levels generally decrease with age in men. This trend may be attributed to reduced liver regenerative capacity or changes in hepatic enzyme activity as part of the natural aging process[54]. In women, the pattern of ALT levels is more complex and appears to be significantly influenced by menopausal status. Studies have shown that post-menopausal women might have higher ALT levels than pre-menopausal women. Additionally, post-menopausal women exhibit decreased ALT levels in the later post-menopausal stage; this is possibly attributable to decreased estrogen levels, which lead to changes in liver fat metabolism and increased inflammation[55]. Furthermore, elevated ALT levels are consistently associated with higher BMI across various racial and ethnic groups, highlighting obesity as a critical predictor of liver enzyme elevations[56]. Studies on adolescents have shown a significant role for ethnic backgrounds in this relationship, in that Hispanic ethnicity is associated with higher BMI and increased odds of obesity[57]. The complex interplay between genetic, demographic, and environmental factors is crucial for tailoring management and prevention strategies for MAFLD across different populations. Diagnostic criteria or algorithms that incorporate personalized ALT thresholds based on age, gender, and BMI might improve the accuracy of MAFLD diagnoses.

Chen *et al*[50] employed a comprehensive approach by using long-term, dynamic, and continuous accumulation of ALT to analyze its relationship with the incidence of MAFLD, which enabled monitoring of changes and patterns in ALT levels over an extended period rather than reliance on single, static measurements. Using a retrospective cohort study design, the authors utilized a large sample size of 3553 participants who were followed through four consecutive health examinations over four years. Their findings showed that sustained alterations in ALT levels could be indicative of the onset of MAFLD. The study is notable for its detailed analysis of the incremental risks associated with different quartiles of ALT levels, employing both equally and unequally weighted cumulative effects. By using cox proportional hazards regression models, the study underscored the importance of monitoring ALT levels within the high-normal range as a potential indicator of MAFLD. This research contributes to a growing body of evidence suggesting that the normal range of ALT levels might need re-evaluation or adjustment based on broader epidemiological data, particularly considering the global rise in metabolic diseases. Moreover, it highlights a significant public health concern, given a large proportion of participants with MAFLD had normal ALT levels, suggesting that relying solely on ALT levels for liver health assessment might lead to at-risk individuals being overlooked. This study extends our understanding of ALT as a

biomarker for liver health, particularly in asymptomatic individuals, and demonstrates the need for diagnostic criteria that consider long-term and cumulative measurements. Further, ALT level was demonstrated as an independent predictor of NASH in NAFLD patients[58,59]. Regular ALT screening enables the timely detection and management of MAFLD progression to severe stages, including NASH, cirrhosis, or even HCC. Early intervention can prevent these severe outcomes.

In turn, the occurrence of MAFLD may increase the risk of ALT elevation. A study investigating the relationship between MAFLD occurrence and ALT elevation through the application of the random intercept cross-lagged panel model revealed that the occurrence of MAFLD was more likely to increase the risk of ALT elevation, suggesting that MAFLD was a stronger predictor of subsequent ALT elevation than the reverse relationship[60].

FUTURE DIRECTIONS AND RESEARCH

The increased incidence of MAFLD is becoming a growing concern. Debates and uncertainties underscore the evolving landscape of MAFLD diagnosis and emphasize the need for ongoing research, discussion, and collaboration to address the complexities and diagnostic challenges associated with this condition. We advocate for integrating ALT screening with other diagnostic methods to improve MAFLD detection, and for continued research to discover more specific and sensitive biomarkers, particularly for identifying early stages of MAFLD and tracking changes in liver fat content and fibrosis over time. These efforts can enhance disease monitoring, management, and treatment effectiveness.

CONCLUSION

MAFLD-a significant public health issue whose incidence continues to increase with the growing obesity epidemic-is associated with various severe health conditions and increased risk of early mortality. The cumulative effects of elevated ALT could be considered as an indicator in identifying new-onset MAFLD. Significant research efforts are underway to identify simple blood-based indicators and other non-invasive approaches for early detection of the disease in the general population and ultimately to improve widespread liver health surveillance and management.

FOOTNOTES

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REFERENCES

1 **Ludwig J**, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; **55**: 434-438 [PMID: 7382552]

2 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231 [PMID: 11961152 DOI: 10.1056/NEJMra011775]

3 **Eslam M**, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, Kawaguchi T, Arrese M, Valenti L, Shiha G, Tiribelli C, Yki-Järvinen H, Fan JG, Grønbæk H, Yilmaz Y, Cortez-Pinto H, Oliveira CP, Bedossa P, Adams LA, Zheng MH, Fouad Y, Chan WK, Mendez-Sanchez N, Ahn SH, Castera L, Bugianesi E, Ratziu V, George J. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020; **73**: 202-209 [PMID: 32278004 DOI: 10.1016/j.jhep.2020.03.039]

4 **Liu J**, Ayada I, Zhang X, Wang L, Li Y, Wen T, Ma Z, Bruno MJ, de Knegt RJ, Cao W, Peppelenbosch MP, Ghanbari M, Li Z, Pan Q.

Estimating Global Prevalence of Metabolic Dysfunction-Associated Fatty Liver Disease in Overweight or Obese Adults. *Clin Gastroenterol Hepatol* 2022; **20**: e573-e582 [PMID: 33618024 DOI: 10.1016/j.cgh.2021.02.030]

5 **Williams CD**, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, Landt CL, Harrison SA. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology* 2011; **140**: 124-131 [PMID: 20858492 DOI: 10.1053/j.gastro.2010.09.038]

6 **Huang YP**, Zhang S, Zhang M, Wang Y, Wang WH, Li J, Li C, Lin JN. Gender-specific prevalence of metabolic-associated fatty liver disease among government employees in Tianjin, China: a cross-sectional study. *BMJ Open* 2021; **11**: e056260 [PMID: 34911725 DOI: 10.1136/bmjopen-2021-056260]

7 **Chalasani N**, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ; American Gastroenterological Association; American Association for the Study of Liver Diseases; American College of Gastroenterology. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology* 2012; **142**: 1592-1609 [PMID: 22656328 DOI: 10.1053/j.gastro.2012.04.001]

8 **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: 26707365 DOI: 10.1002/hep.28431]

9 **Sun DQ**, Targher G, Byrne CD, Wheeler DC, Wong VW, Fan JG, Tilg H, Yuan WJ, Wanner C, Gao X, Long MT, Kanbay M, Nguyen MH, Navaneethan SD, Yilmaz Y, Huang Y, Gani RA, Marzuillo P, Boursier J, Zhang H, Jung CY, Chai J, Valenti L, Papatheodoridis G, Musso G, Wong YJ, El-Kassas M, Méndez-Sánchez N, Sookoian S, Pavlides M, Duseja A, Holleboom AG, Shi J, Chan WK, Fouad Y, Yang J, Treeprasertsuk S, Cortez-Pinto H, Hamaguchi M, Romero-Gomez M, Al Mahtab M, Ocama P, Nakajima A, Dai C, Eslam M, Wei L, George J, Zheng MH. An international Delphi consensus statement on metabolic dysfunction-associated fatty liver disease and risk of chronic kidney disease. *Hepatobiliary Surg Nutr* 2023; **12**: 386-403 [PMID: 37351121 DOI: 10.21037/hbsn-22-421]

10 **Tariq R**, Axley P, Singal AK. Extra-Hepatic Manifestations of Nonalcoholic Fatty Liver Disease: A Review. *J Clin Exp Hepatol* 2020; **10**: 81-87 [PMID: 32025167 DOI: 10.1016/j.jceh.2019.07.008]

11 **Li AA**, Ahmed A, Kim D. Extrahepatic Manifestations of Nonalcoholic Fatty Liver Disease. *Gut Liver* 2020; **14**: 168-178 [PMID: 31195434 DOI: 10.5009/gnl19069]

12 **Rinella ME**, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, Loomba R. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023; **77**: 1797-1835 [PMID: 36727674 DOI: 10.1097/HEP.0000000000000323]

13 **Dasarathy S**, Dasarathy J, Khiyami A, Joseph R, Lopez R, McCullough AJ. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. *J Hepatol* 2009; **51**: 1061-1067 [PMID: 19846234 DOI: 10.1016/j.jhep.2009.09.001]

14 **Eddowes PJ**, Sasso M, Allison M, Tsochatzis E, Anstee QM, Sheridan D, Guha IN, Cobbold JF, Deeks JJ, Paradis V, Bedossa P, Newsome PN. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2019; **156**: 1717-1730 [PMID: 30689971 DOI: 10.1053/j.gastro.2019.01.042]

15 **Reeder SB**, Cruite I, Hamilton G, Sirlin CB. Quantitative Assessment of Liver Fat with Magnetic Resonance Imaging and Spectroscopy. *J Magn Reson Imaging* 2011; **34**: 729-749 [PMID: 22025886 DOI: 10.1002/jmri.22775]

16 **Mofrad P**, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology* 2003; **37**: 1286-1292 [PMID: 12774006 DOI: 10.1053/jhep.2003.50229]

17 **Park H**, Yoon EL, Kim M, Lee J, Cho S, Jun DW, Nah EH. Reappraisal of fibrosis-4 index and non-alcoholic fatty liver disease fibrosis score for advanced fibrosis in average-risk population. *Front Med (Lausanne)* 2022; **9**: 1024836 [PMID: 36405611 DOI: 10.3389/fmed.2022.1024836]

18 **Sugiyama A**, Kurisu A, E B, Ouoba S, Ko K, Rakhimov A, Akita T, Harakawa T, Sako T, Koshiyama M, Kumada T, Tanaka J. Distribution of FIB-4 index in the general population: analysis of 75,666 residents who underwent health checkups. *BMC Gastroenterol* 2022; **22**: 241 [PMID: 35562658 DOI: 10.1186/s12876-022-02290-1]

19 **Wang YJ**, Jin CH, Ke JF, Wang JW, Ma YL, Lu JX, Li MF, Li LX. Decreased Serum Osteocalcin is an Independent Risk Factor for Metabolic Dysfunction-Associated Fatty Liver Disease in Type 2 Diabetes. *Diabetes Metab Syndr Obes* 2022; **15**: 3717-3728 [PMID: 36471670 DOI: 10.2147/DMSO.S389794]

20 **Liu Y**, Liu S, Huang J, Zhu Y, Lin S. Validation of five hepatic steatosis algorithms in metabolic-associated fatty liver disease: A population based study. *J Gastroenterol Hepatol* 2022; **37**: 938-945 [PMID: 35174539 DOI: 10.1111/jgh.15799]

21 **European Association for the Study of the Liver (EASL)**; European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; **64**: 1388-1402 [PMID: 27062661 DOI: 10.1016/j.jhep.2015.11.004]

22 Non-Alcoholic Fatty Liver Disease: Assessment and Management. London: National Institute for Health and Care Excellence (NICE); 2016 Jul- [PMID: 27441333]

23 **Wong VW**, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, Fan J, Goh KL, Hamaguchi M, Hashimoto E, Kim SU, Lesmana LA, Lin YC, Liu CJ, Ni YH, Sollano J, Wong SK, Wong GL, Chan HL, Farrell G. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 1: Definition, risk factors and assessment. *J Gastroenterol Hepatol* 2018; **33**: 70-85 [PMID: 28670712 DOI: 10.1111/jgh.13857]

24 **Leoni S**, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. *World J Gastroenterol* 2018; **24**: 3361-3373 [PMID: 30122876 DOI: 10.3748/wjg.v24.i30.3361]

25 **Pandyarajan V**, Gish RG, Alkhouri N, Noureddin M. Screening for Nonalcoholic Fatty Liver Disease in the Primary Care Clinic. *Gastroenterol Hepatol (N Y)* 2019; **15**: 357-365 [PMID: 31391806]

26 **Schindhelm RK**, Diamant M, Dekker JM, Tushuizen ME, Teerlink T, Heine RJ. Alanine aminotransferase as a marker of non-alcoholic fatty liver disease in relation to type 2 diabetes mellitus and cardiovascular disease. *Diabetes Metab Res Rev* 2006; **22**: 437-443 [PMID: 16832839 DOI: 10.1002/dmrr.666]

27 **Burgert TS**, Taksali SE, Dziura J, Goodman TR, Yeckel CW, Papademetris X, Constable RT, Weiss R, Tamborlane WV, Savoye M, Seyal AA, Caprio S. Alanine aminotransferase levels and fatty liver in childhood obesity: associations with insulin resistance, adiponectin, and visceral fat. *J Clin Endocrinol Metab* 2006; **91**: 4287-4294 [PMID: 16912127 DOI: 10.1210/jc.2006-1010]

28 **Cusi K**. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications.

Gastroenterology 2012; **142**: 711-725.e6 [PMID: 22326434 DOI: 10.1053/j.gastro.2012.02.003]
29 **Maximos M**, Bril F, Portillo Sanchez P, Lomonaco R, Orsak B, Biernacki D, Suman A, Weber M, Cusi K. The role of liver fat and insulin resistance as determinants of plasma aminotransferase elevation in nonalcoholic fatty liver disease. *Hepatology* 2015; **61**: 153-160 [PMID: 25145475 DOI: 10.1002/hep.27395]
30 **Park SH**, Seo W, Xu MJ, Mackowiak B, Lin Y, He Y, Fu Y, Hwang S, Kim SJ, Guan Y, Feng D, Yu L, Lehner R, Liangpunsakul S, Gao B. Ethanol and its Nonoxidative Metabolites Promote Acute Liver Injury by Inducing ER Stress, Adipocyte Death, and Lipolysis. *Cell Mol Gastroenterol Hepatol* 2023; **15**: 281-306 [PMID: 36243320 DOI: 10.1016/j.jcmgh.2022.10.002]
31 **Yu LH**, Yu WL, Zhao T, Wu MC, Fu XH, Zhang YJ. Post-operative delayed elevation of ALT correlates with early death in patients with HBV-related hepatocellular carcinoma and Post-hepatectomy Liver Failure. *HPB (Oxford)* 2018; **20**: 321-326 [PMID: 29373299 DOI: 10.1016/j.hpb.2017.10.001]
32 **Falck-Ytter Y**, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis* 2001; **21**: 17-26 [PMID: 11296693 DOI: 10.1055/s-2001-12926]
33 **Clark JM**, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003; **98**: 960-967 [PMID: 12809815 DOI: 10.1111/j.1572-0241.2003.07486.x]
34 **Kaplan MM**. Alanine aminotransferase levels: what's normal? *Ann Intern Med* 2002; **137**: 49-51 [PMID: 12093245 DOI: 10.7326/0003-4819-137-1-200207020-00012]
35 **Degertekin B**, Tozun N, Demir F, Soylemez G, Yapali S, Bozkurt U, Gurtay E, Seymenoglu TH, Mutlu D, Toraman M. Determination of the upper limits of normal serum alanine aminotransferase (ALT) level in healthy Turkish population. *Hepatol Forum* 2020; **1**: 44-47 [PMID: 35949438 DOI: 10.14744/hf.2020.2020.0012]
36 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. *Clin Liver Dis (Hoboken)* 2018; **12**: 33-34 [PMID: 30988907 DOI: 10.1002/cld.728]
37 **European Association for the Study of the Liver**. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]
38 **Cusi K**, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, Kashyap S, Mechanick JI, Mouzaki M, Nadolsky K, Rinella ME, Vos MB, Younossi Z. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract* 2022; **28**: 528-562 [PMID: 35569886 DOI: 10.1016/j.eprac.2022.03.010]
39 **Koutoukidis DA**, Koshiaris C, Henry JA, Noreik M, Morris E, Manoharan I, Tudor K, Bodenham E, Dunnigan A, Jebb SA, Aveyard P. The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Metabolism* 2021; **115**: 154455 [PMID: 33259835 DOI: 10.1016/j.metabol.2020.154455]
40 **Jirapinyo P**, McCarty TR, Dolan RD, Shah R, Thompson CC. Effect of Endoscopic Bariatric and Metabolic Therapies on Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2022; **20**: 511-524.e1 [PMID: 33727164 DOI: 10.1016/j.cgh.2021.03.017]
41 **Bajaj HS**, Burrows M, Blavignac J, Paron E, Camacho F, Gould E, Barakat M. Extended-release naltrexone/bupropion and liver health: Pooled, post hoc analysis from four randomized controlled trials. *Diabetes Obes Metab* 2021; **23**: 861-865 [PMID: 33275326 DOI: 10.1111/dom.14284]
42 **Mota M**, Banini BA, Cazanave SC, Sanyal AJ. Molecular mechanisms of lipotoxicity and glucotoxicity in nonalcoholic fatty liver disease. *Metabolism* 2016; **65**: 1049-1061 [PMID: 26997538 DOI: 10.1016/j.metabol.2016.02.014]
43 **Musso G**, Cassader M, Paschetta E, Gambino R. Bioactive Lipid Species and Metabolic Pathways in Progression and Resolution of Nonalcoholic Steatohepatitis. *Gastroenterology* 2018; **155**: 282-302.e8 [PMID: 29906416 DOI: 10.1053/j.gastro.2018.06.031]
44 **Liangpunsakul S**, Chalasani N. Lipid mediators of liver injury in nonalcoholic fatty liver disease. *Am J Physiol Gastrointest Liver Physiol* 2019; **316**: G75-G81 [PMID: 30383414 DOI: 10.1152/ajpgi.00170.2018]
45 **Geng Y**, Faber KN, de Meijer VE, Blokzijl H, Moshage H. How does hepatic lipid accumulation lead to lipotoxicity in non-alcoholic fatty liver disease? *Hepatol Int* 2021; **15**: 21-35 [PMID: 33548031 DOI: 10.1007/s12072-020-10121-2]
46 **Alkhouri N**, Tamimi TA, Yerian L, Lopez R, Zein NN, Feldstein AE. The inflamed liver and atherosclerosis: a link between histologic severity of nonalcoholic fatty liver disease and increased cardiovascular risk. *Dig Dis Sci* 2010; **55**: 2644-2650 [PMID: 19960252 DOI: 10.1007/s10620-009-1075-y]
47 **Bianco C**, Casirati E, Malvestiti F, Valenti L. Genetic predisposition similarities between NASH and ASH: Identification of new therapeutic targets. *JHEP Rep* 2021; **3**: 100284 [PMID: 34027340 DOI: 10.1016/j.jhepr.2021.100284]
48 **Amarapurkar DN**, Patel ND. Clinical spectrum and natural history of non-alcoholic steatohepatitis with normal alanine aminotransferase values. *Trop Gastroenterol* 2004; **25**: 130-134 [PMID: 15682660]
49 **Ma X**, Liu S, Zhang J, Dong M, Wang Y, Wang M, Xin Y. Proportion of NAFLD patients with normal ALT value in overall NAFLD patients: a systematic review and meta-analysis. *BMC Gastroenterol* 2020; **20**: 10 [PMID: 31937252 DOI: 10.1186/s12876-020-1165-z]
50 **Chen JF**, Wu ZQ, Liu HS, Yan S, Wang YX, Xing M, Song XQ, Ding SY. Cumulative effects of excess high-normal alanine aminotransferase levels in relation to new-onset metabolic dysfunction-associated fatty liver disease in China. *World J Gastroenterol* 2024; **30**: 1346-1357 [PMID: 38596503 DOI: 10.3748/wjg.v30.i10.1346]
51 **Huang DQ**, Yeo YH, Tan E, Takahashi H, Yasuda S, Saruwatari J, Tanaka K, Oniki K, Kam LY, Muthiah MD, Hyogo H, Ono M, Barnett SD, Li J, Zou B, Fung J, Lee TY, Wong VW, Yuen MF, Dan YY, Lim SG, Cheung R, Toyoda H, Eguchi Y, Nguyen MH. ALT Levels for Asians With Metabolic Diseases: A Meta-analysis of 86 Studies With Individual Patient Data Validation. *Hepatol Commun* 2020; **4**: 1624-1636 [PMID: 33163833 DOI: 10.1002/hep4.1593]
52 **Valenti L**, Pelusi S, Bianco C, Ceriotti F, Berzuini A, Iogna Prat L, Trotti R, Malvestiti F, D'Ambrosio R, Lampertico P, Colli A, Colombo M, Tsochatzis EA, Fraquelli M, Prati D. Definition of Healthy Ranges for Alanine Aminotransferase Levels: A 2021 Update. *Hepatol Commun* 2021; **5**: 1824-1832 [PMID: 34520121 DOI: 10.1002/hep4.1794]
53 **Wu ZY**, Chi SW, Ouyang LJ, Xu XQ, Chen JN, Jin BH, Ullah R, Zhou XL, Huang K, Dong GP, Li ZM, Shen Y, Shao J, Ni Y, Fu JF, Shu Q, Wu W. Continuous age- and sex-specific reference ranges of liver enzymes in Chinese children and application in pediatric non-alcoholic fatty liver disease. *World J Pediatr* 2024 [PMID: 38388968 DOI: 10.1007/s12519-023-00789-5]
54 **Dong MH**, Bettencourt R, Brenner DA, Barrett-Connor E, Loomba R. Serum levels of alanine aminotransferase decrease with age in longitudinal analysis. *Clin Gastroenterol Hepatol* 2012; **10**: 285-90.e1 [PMID: 22020064 DOI: 10.1016/j.cgh.2011.10.014]

55 **Matsui S**, Yasui T, Kasai K, Keyama K, Kato T, Uemura H, Kuwahara A, Matsuzaki T, Irahara M. Changes of liver enzymes and triglyceride during the menopausal transition in Japanese women. *J Obstet Gynaecol* 2016; **36**: 806-811 [PMID: 27167882 DOI: 10.3109/01443615.2016.1154516]

56 **Ruhl CE**, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* 2003; **124**: 71-79 [PMID: 12512031 DOI: 10.1053/gast.2003.50004]

57 **Kirby JB**, Liang L, Chen HJ, Wang Y. Race, place, and obesity: the complex relationships among community racial/ethnic composition, individual race/ethnicity, and obesity in the United States. *Am J Public Health* 2012; **102**: 1572-1578 [PMID: 22698012 DOI: 10.2105/AJPH.2011.300452]

58 **Torres DM**, Harrison SA. NAFLD: Predictive value of ALT levels for NASH and advanced fibrosis. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 510-511 [PMID: 23897284 DOI: 10.1038/nrgastro.2013.138]

59 **Verma S**, Jensen D, Hart J, Mohanty SR. Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). *Liver Int* 2013; **33**: 1398-1405 [PMID: 23763360 DOI: 10.1111/liv.12226]

60 **Chen JF**, Wu ZQ, Yan S, Wang YX, Song XQ, Ding SY. [The bidirectional relationship between long-term dynamic alanine aminotransferase level and metabolic associated fatty liver disease]. *Zhonghua Neifenmi Daixie Zazhi* 2023; **39**: 1028-1036

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