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EDITORIAL

# Effects of excess high-normal alanine aminotransferase levels in relation to new-onset metabolic dysfunction-associated fatty liver disease: Clinical implications

Giovanna McGinty, Robert Przemioslo

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## Abstract

In this editorial, we comment on the article by Chen *et al* recently published in 2024. We focus the debate on whether reducing the upper limit of normal of alanine aminotransferase (ALT) would effectively identify cases of fibrosis in metabolic-dysfunction associated fatty liver disease (MAFLD). This is important given the increasing prevalence of MAFLD and obesity globally. Currently, a suitable screening test to identify patients in the general population does not exist and most patients are screened after the finding of an abnormal ALT. The authors of this paper challenge the idea of what a normal ALT is and whether that threshold should be lowered, particularly as their study found that 83.12% of their study population with a diagnosis of MAFLD had a normal ALT. The main advantages of screening would be to identify patients and provide intervention early, the mainstay of this being changing modifiable risk factors and monitoring for liver fibrosis. However, there is not enough suitable therapeutic options available as of yet although this is likely to change in the coming years with more targets for therapy being discovered. Semaglutide is one example of this which has demonstrated benefit with an acceptable side effect profile for those patients with MAFLD and obesity, although studies have not yet shown a significant improvement in fibrosis regression. It would also require a huge amount of resource if a reduced ALT level alone was used as criteria; it is more likely that current scoring systems such as fibrosis-4 may be amended to represent this additional risk. Currently, there is not a good argument to recommend widespread screening with a reduced ALT level as this is unlikely to be cost-effective. This is compounded by the fact that there is a significant heterogeneity in what is considered a normal ALT between laboratories. Although studies previously have suggested a more pragmatic approach in screening those over the age of 60, this is

likely to change with the increasing incidence of obesity within the younger age groups. The main message from this study is that those who have hypercholesterolemia and high body metabolic index should have these risk factors modified to maintain a lower level of ALT to reduce the risk of progression to fibrosis and cirrhosis.

**Key Words:** Alanine aminotransferase; Metabolic-dysfunction associated fatty liver disease; Metabolic syndrome; Fibrosis; Cirrhosis; Semaglutide



**Core Tip:** Alanine aminotransferase (ALT) is a surrogate marker for metabolic-dysfunction associated fatty liver disease (MAFLD) but is not specific for histological inflammation. The rationale to reduce the upper limit of normal for ALT to help identify more cases of MAFLD remains controversial. It is more important to identify patients who may display elements of the metabolic syndrome and support modifying these to maintain a lower level of ALT. This will become increasingly important as more targets for therapy are identified that may justify treating these patients early to prevent progression to fibrosis.

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## INTRODUCTION

Metabolic-dysfunction associated fatty liver disease (MAFLD) is the most common liver disease worldwide with a current prevalence of around 25% in the Western world and rising[1]. Obesity, type 2 diabetes mellitus (T2DM), hypertension and dyslipidemia are established risk factors for the development of MAFLD. Elevation in alanine aminotransferase (ALT) is an associated biomarker of the metabolic syndrome[2]. It also has an association with serum triglycerides, plasma fasting glucose and body metabolic index. The prevalence of MAFLD has increased considerably in the last few years and will continue to increase due to the increasing prevalence of obesity and the metabolic syndrome. The morbidity related to MAFLD is also significant: It can increase the risk of cardiovascular disease and increase the cancer-related mortality[3]. This rising incidence that has been observed and the parallel with obesity will likely cause an increase in the aforementioned causes of morbidity.

ALT has previously been shown to be an independent predictor of the development of fibrosis and is a marker of hepatocellular injury[4,5]. However, ALT is not specific for histological inflammation, nor can it help determine whether cirrhosis is likely to be present[6]. MAFLD has been shown to occur in the presence of a normal ALT[7]. It is often the case that advanced fibrosis is seen in patients with normal ALT in MAFLD. Currently, there is no recommendation to screen for MAFLD in the asymptomatic population although this has gained more attention in recent times[8]. A recent study by Lomonaco *et al*[9] suggests we should be more proactive in screening patients with T2DM since the authors found that 15% of patients of those with T2DM had F2 or higher fibrosis. It is not known whether there is a level of ALT where we should consider screening for MAFLD. The data from Chen *et al*[10] sought to answer this question.

In the study by Chen *et al*[10], the authors reported on a retrospective and prospective population-based cohort study in China. A similar study has been performed in the pediatric population to help determine an optimal cut-off for ALT [11]. The patients were aged over 18-year-old and were selected over a consecutive period of 3 years between January 2017 and December 2019. 3553 participants were found to be eligible from their initial pool of 7817 participants. The authors used a combination of physical measurements, laboratory test results, Doppler ultrasound measurements and established diagnostic criteria for MAFLD.

The authors used a receiver operating characteristic curve with the maximum value of the Youden index to determine the ALT cut-off point, in line with other similar studies[12,13]. The cumulative effect of this was found to be significant compared to those that only had a single occurrence of an ALT > 18.5 U/L. It has been shown in a prospective study by Gawrieh *et al*[14] that advanced fibrosis and steatohepatitis increases in frequency when ALT increases from 20 U/L to 39 U/L. The authors of the study by Chen *et al*[10] were able to demonstrate that 83.12% of the participants with MAFLD had a normal ALT. They also concluded that the risk of developing MAFLD is related to a persistently high ALT leading to a cumulative effect. This supports other studies that have found that a persistently raised ALT can lead to significant fibrosis from MAFLD[15,16].

## SHOULD WE BE SCREENING FOR MAFLD AT A LOWER ALT?

As of 2022, MAFLD affected one-third of the global population[17]. The diagnosis of MAFLD is made by the presence of

hepatic steatosis and the presence of one or more of the elements of the metabolic syndrome[18]. Hepatocellular damage releases ALT, with MAFLD being the most common cause of asymptomatic elevation of transaminase levels. With a significant morbidity associated with this, the most important being cardiovascular disease, we should be examining whether a suitable screening test exists to pick up those asymptomatic patients that would benefit from early intervention.

The Chen *et al*[10] study provides the argument that the cut-off for abnormal ALT should be reduced to 18.5 U/L, which is lower than the level typically used to start investigating for the presence of MAFLD in clinical practice, at least in the United Kingdom. If this definition was adopted widely, investigating individuals with this level of ALT would require a significant amount of extra resource to manage the workload of identifying and managing these patients. This should be balanced with the cost related to health-related complications that can eventually occur, such as hospitalization from cardiovascular events, decompensated liver disease and hepatocellular carcinoma. It has been argued previously that the demographic most likely to benefit from screening for MAFLD would be those aged older than 60 due to the increased mortality in this age group[19]. However, this is likely to change with the increasing incidence of obesity seen at younger ages[20]. There has been some debate on whether screening should be employed, on which patients and how. The American Association for the Study of Liver Diseases argue that there is simply not a cost-effective method to do this routinely and should only be performed in specific population groups[21].

There is a lack of effective pharmacological solutions to managing MAFLD. The mainstay of management currently is in the managing of metabolic risk factors and working closely with endocrinologists and cardiologists as necessary to help prevent disease progression. However, the landscape of pharmacological treatments is changing and much research is ongoing to establish new targets for therapy[22]. Semaglutide, a glucagon-like peptide-1 receptor agonist which is used to treat diabetes and obesity, has shown some promising initial results for treating MAFLD whilst also being well-tolerated. However, there have not been enough large randomized controlled trials to date to suggest that it significantly reverses biochemistry or causes fibrosis regression[23].

The current practice is that ALT is usually combined with other markers to give a predictor of fibrosis to which a clinician may investigate further by magnetic resonance imaging, transient elastography or liver biopsy. Fibrosis-4 and enhanced liver fibrosis scores are the most widely used non-invasive screening tests[24] and it may be in time, the ALT level that contributes to this is lowered to reflect the evidence that MAFLD can occur in the presence of a traditionally "normal" ALT. However, it is not clear currently that doing this routinely would be cost-effective or lead to a lower mortality necessarily given the lack of treatment options that exist currently.

## CONCLUSION

A cumulative higher level of ALT, whether that is upper limit of normal or above this, can present an additional risk factor for the development of MAFLD. There is currently no consensus on how we should screen asymptomatic patients for MAFLD due to lack of therapeutic options and being able to prevent disease progression consistently. The question is not whether MAFLD can be diagnosed with a normal ALT: It is what we define as a normal ALT. This study suggests that MAFLD can occur at a lower level than we would typically flag as "abnormal". The high prevalence and morbidity should give us the motivation to keep searching the answers to these questions. As clinicians, we should be more astute to those that may have typical risk factors but have a normal ALT; perhaps we should have a lower threshold for screening these patients. It is likely to be more important to support patients in changing modifiable risk factors to maintain a lower level of ALT.

## FOOTNOTES

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